CONSTITUTION AND DISEASE

Applied Constitutional Pathology

BY

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SECOND EDITION
REVISED AND ENLARGED



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U S A

PREFACE TO THE FIRST EDITION

MANY of the American postgraduate students who took courses with me at the University of Vienna (Austria) between 1923 and 1938 asked me to write a book on the subject of my lectures. The participants in my last European postgraduate course, given at the American Hospital in Paris in the summer of 1938, and particularly my friend Dr. Lawrence S. Fuller, at that time head of the medical department of the hospital, urged me again to make the lectures available to the American profession. I promised to do so, if possible. The lectures covered the subject "Endocrinology and Constitutional Pathology."

There is no need for a textbook on endocrinology in this country. There may, however, be a need for some instruction on how to correlate the facts taught in endocrinology, and in other branches of medicine as well, to the particular situation encountered in individual patients. This is what might be called "applied constitutional pathology." What was new and attractive to my American students in Europe was not another compilation of facts, but another way of interpreting them in their application to individual cases; it was the way of taking into consideration not one or several organs of the patient, but his whole personality, both physical and mental; it was the adaptation of genetics to clinical problems considered to be chiefly endocrinologic in nature; it was the conviction that all available tests and laboratory studies, invaluable as they might be, can never replace the impression gathered from an intelligent observation of the patient himself.

America has taken the leadership in medicine as well as in technical and biologic sciences. This was expressed as early as 1930 after my second visit to the United States.* In so

* BAUER, J. Was erwartet europäische Ärzte in Nord-Amerika? Wien. med. Wchnschr. no. 15, 1930.

far, however, as medicine is more than applied exact science and as it requires an integrative comprehension of the patient's personality, it might be well not to overlook the artistic trend of medicine as taught in central Europe, particularly in Vienna and Paris, in prewar times I am happy to be in full accord in this regard with W R Houston and other authorities in our country Tucker and Lessa of the University of Chicago expressed it as follows

In Europe, particularly in Germany, Austria, Italy, and France, where the tradition of the endogenous constitutional factors lived in many of the older physicians and scientists, the newer interest in exogenous factors never entirely displaced the constitutional approach to biological problems. In the United States, however, with modern medical schools developing only since the time of Pasteur, the absence of the older constitutional tradition has been felt and evidenced in the almost entire absence of a consideration of constitution in medicine

It is taken for granted—usually without particular amazement—that the potential energy of the germ plasm accounts for the development of a full fledged human being out of a fertilized human ovum of microscopic proportions in the short period of nine months It is not adequately realized, however, that this potential energy is at work throughout a whole lifetime, that the physiologic evolution and involution, the structure and function of the organs, their mutual relation, and the response to various stimuli depend on this potential energy, that deficiencies and abnormalities of this potential energy may be cooperative etiologic factors or the sole cause of diseases, that they account for the vast majority of congenital malformations in man *And this potential energy is just what we may call individual constitution* The great miracle of this potential energy is fully recognized as far as the fetal development is concerned, *but the miracle is not over with the moment of birth*

The general dislike of speculative approach to biologic problems is justified—but only so far as it is not sufficiently sup-

ported by facts On the other hand, the accumulation of facts

of facts is as little a science as a heaping up of stones is a house

My way of looking at nature and facts is not free from every author's "unavoidable tendency to twist and simplify according to the ineradicable conditions of his mental processes" (S Ramón y Cajal) It seems, however, that this way is in closest accord with the facts, and it is inevitable though neglected

No attempt has been made to compile all or even most of the literature on the subject of human constitution It was intended instead to familiarize the reader with the principles of "constitutional thinking" at the patient's bedside It must not be taken as lack of modesty if the work done by the writer and his former collaborators in Vienna in the last thirty years is referred to more frequently and extensively than the work of other authors This fact results quite naturally from the personal rather than compilatory character of the book Case histories were added only if they seemed to illustrate certain facts better than circumstantial theoretic discussions They have been recorded only as far as they serve this purpose, briefly and with omission of immaterial details

Thus this little book may stimulate medical thinking and

objectives it may contribute to the ultimate aim of medicine *to help the sick, or, as Trudeau used to say, to* cure sometimes, to relieve often, to comfort always

Los Angeles, July 1942 JULIUS BAUER

PREFACE TO THE SECOND EDITION

THE fact that a second edition of this book is called for a year and a half after its first publication implies at least a sustained interest in the original effort and perhaps reflects a growing recognition of the need of such a text

Reviews and comment from professional organs and among individual readers have given proof of almost universally favorable reception of the book An editorial given to it in the *British Medical Journal*, and the publication of a Portuguese translation in Rio de Janeiro in 1943 and of a Spanish translation in Buenos Aires in the same year, would indicate that the need for a book of this type is likewise perceived in other countries of both hemispheres

For the new edition certain amplifications of the text have been made and new citations covering the most recent literature constitute a considerable addition to the bibliography The volume is now also equipped with an index facilitating convenience of use for both the scientific investigator and the medical practitioner

The book should continue to have valid function since it is felt—and the realization is reflected from various perspectives besides my own—that up to now too little attention has been given to the constitutional or genetic standpoint in both general and specialized practice of medicine particularly in clinical endocrinology Certain clinical syndromes have been reported and interpreted on the basis of endocrinologic considerations only To discount or neglect the constitutional aspects of such syndromes may lead the diagnostician or the research worker astray from basic paths as regards both etiologic discrimination and therapeutic effectiveness

Whether or not the various opinions expressed in this study are correct or may require modification remains for the future to determine. It is certain, however, that the problems it formulates must be taken into consideration by all who are concerned with the elucidation of true or apparent endocrinologic disturbances in human beings.

For the general practitioner, the discussion may give substance to the idea expressed in the aphorism of an English reviewer: "In clinical medicine the laboratory is a good servant but a bad master."

JULIUS BAUER

Los Angeles, January 1945

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I

INTRODUCTION

1 The Science and Art of Medicine

The science of medicine deals with diseases We define disease as an abnormal course of a vital process producing impairment of the individual and diminishing his fitness and efficiency It may or may not be accompanied by subjective sensations of discomfort Diseases are classified and labeled from the point of view of a uniform etiology or pathology Yet in different patients the disturbance of any vital process, although caused by the same etiologic factors and associated with the same pathologic alterations, may show considerable variation in the clinical picture and course

It is common knowledge that no two individuals are ever completely alike We observe these differences in the general appearance and in details of face, hands, gait, voice, behavior, handwriting, etc The laboratory data that we use in daily practice have to be evaluated from normal physiologic standards that show a wide range for each value The pulse rate, blood pressure, blood count, gastric acidity, the various figures for blood chemistry, should be considered in the light of individual variability under normal conditions The same holds true for the adaptative and reserve power of each organ, for the regenerative capacity of tissues, for the mobilization of defenses against invading bacteria or poisons, for the reaction of the nervous system, and for the resultant subjective sensations that accompany any disturbance of vital balance.

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The art of medicine deals with the consideration of such individual differences and their bearing upon both diagnosis and treatment

2 Normal and Abnormal

What should be considered the limits of normality? To establish the normal from the average values of each characteristic is very difficult, morphologically, functionally, and chemically Stockard[1] states correctly· "Every observer soon learns from even limited experience with numbers of living animals that the average individual is rare or nonexistent, this average being only a theoretical mean of deviations in many directions" In this connection, it is interesting to learn for instance that the greater splanchnic nerve has been found "normal" in only 23 per cent of all individuals examined at random[2] This was stated on the basis of a liberal interpretation of normality On the basis of a strict application of the typical textbook descriptions of normalcy, only 9 per cent of individuals examined at random were found to have a normal greater splanchnic nerve These studies of Edwards illustrate how great are the anatomic variations in human beings and with how much discretion the term "normal" should be applied

The clinical frequency of certain individual variations was studied in Vienna[3] Such variations included unusual proportions of the body or of some of its parts, developmental anomalies, such as uvula bifida, supernumerary mammillae, partial syndactylism, irregularity of dentition, unusual distribution of hair, arched palate, hyperextensibility of certain joints, unusual responses of the nervous system to stimuli, such as absence of corneal and pharyngeal reflexes, a pseudo Babinski phenomenon, high grade Chvostek sign, etc Of 263 persons examined, not one was free of all of these variations, the majority exhibited five such variations from the accepted normal average

A similar result was obtained in the study of such variations

in the Negro population of New Orleans[4] As only less frequent variations from the average were recorded in this series, we found that only 15 per cent of the male and 35 per cent of the female Negroes did not show any of the deviations from the supposed normal average The majority of the persons examined exhibited one or two and many of them more than two signs of deviation from the supposed normal average

There is need for a more accurate definition of the term normal and a delineation of the limits of both the normal and the abnormal[5] As a matter of fact, such definitions can apply only to particular characteristics and not to the individual as a whole If a particular variation of a certain trait is found in less than 4 5 per cent of all individuals of the population, then it should be called abnormal, if it is found more frequently than in 4 5 per cent of the population, it should be considered normal, although a deviation from the average The rationale for such a delimitation of normal and abnormal will be given in a later chapter (p 146) Such a classification is of course arbitrary, but its establishment is necessary for practical purposes, even where sharply defined limits do not exist

Far reaching consequences may and often do result from ignorance of what should be considered abnormal in an electrocardiogram

An electrocardiographic study of 500 apparently healthy young working adults disclosed that half of the records fell *outside* the range of normal on the basis of authoritative electrocardiographic criteria of *normality* in current general use The implication is that electrocardiographic surveys will be misleading unless criteria of what is normal are revised and broadened (Viscidi and Geiger)[12 13]

3 Causes of Individual Variability

The main cause of individual variability lies in sexual mating The discovery made in 1865 by the Austrian monk Gregor Mendel has become the foundation of the science of genetics, which has given us a thorough understanding of the

principles underlying individual variability. Constant segregation and redistribution of characteristics in the continuous stream of life formed by the germ plasm account for the uniqueness of the individual personality. August Weismann was the first to emphasize the continuity of the germ plasm, from which generations arise and die away. Each individual represents a host for the germinal material, but in an ever new and never before existing combination of hereditary units, each of which is handed down to the particular individual from the previous generation. This doctrine, growing out of the experience of breeders and experimental geneticists, has obtained a material substratum from the research work done in cytology. Sutton, of Columbia University, was the first to emphasize the probable correlation between the cytologic phenomena observed in mitotic cell division and the mendelian laws derived from experiments in genetics. The cytologic facts observed exactly fit the demands of the mendelian laws.

As a matter of fact, hereditary units or genes themselves are merely potential energies and can act only under conditions supplied by the environment. These conditions involve the necessary amount and quality of building material—that is, of foodstuff—the necessary amount of oxygen, the correct temperature, humidity, etc. These general environmental conditions are provided under the usual circumstances existing during the intra-uterine and extra-uterine development of human beings. Gross modifications of the environmental conditions, as they are artificially produced in laboratories for experimental purposes, occur in the case of humans only by exception. Shortage of food, particularly of certain vitamins, or insufficiency of oxygen supply to the tissues, and similar environmental influences, may occur in humans both as causal factors and as consequences of disease. Generally, however, the environmental conditions necessary for full activity of the hereditary factors are provided to approximately the same extent in all healthy human individuals.

Of greater importance is the influence of the environment upon the manifestations of those hereditary anlagen that relate to mental functions It is unnecessary to point out in more detail the extent to which education and training influence the psychic characteristics of an individual "Heredity determines what one can do, environment determines what one does do"[6]

4 Identical (Uniovular) Twins

The study of identical or uniovular twins, their morphologic and functional behavior under normal and pathologic conditions, is the most reliable method of evaluating the share of both environmental and genetic influences Identical twins originate from the same fertilized ovum One set of chromosomes is the point of origin for two individuals instead of one No matter what may be the actual reason for such a separation of the germ into two independent halves, the fact is well established that identical twins represent the only exception to the rule that there are no two individuals possessing the same constellation of hereditary units Anthropologic measure-[illegible] shells, [illegible] uovular [illegible] it is difficult sometimes even for the parents to distinguish one twin from the other This striking similarity also extends to such functional characteristics as blood pressure, acidity of the gastric juice, response to a glucose tolerance test, and to many other functional activities and biochemical values Even the voices, the handwritings, and the psychologic traits frequently show a quite surprising similarity The biologic importance of the study of identical twins was first recognized by Galton[7] The value of systematic studies of twin pathology has been emphasized and a great deal of material on this subject has been accumulated since this first study[8] We shall return to this problem later Here we wish merely to stress the fact that, generally speaking, diversities

in identical twins should be considered as due to differences in environmental factors, whereas identity of features bespeaks their identical genetic origin

An interesting illustration of this principle is found in the studies of *body weight in identical twins* Newman *et al*[7] compared the variability of body weight of identical twins with that of so-called fraternal or binovular twins, and with that of nontwin siblings of the same sex Fraternal twins and nontwin siblings showed a very similar variability of body weight, the average pair differences in weight being 10 0 pounds for fraternal twins and 10 4 pounds for nontwin siblings Identical twins exhibited a far more limited variability in body weight, the average pair difference in weight amounting to only 4 1 pounds Only 2 per cent of the identical twins differed by more than 12 pounds in weight, as against 51 5 per cent of the fraternal twins and 53 5 per cent of the nontwin siblings

Von Verschuer[8] reported on a study of fifty-seven pairs of identical twins between the ages of 3 and 51 years Twenty-seven different measurements were taken and their "average *percentual variation*" *determined as follows: The middle* value of a measurement taken on both individuals of a pair of twins was determined, and the deviation from the middle value was expressed in percentage of the middle value The average of these percentual variations for all twins examined was considered the average percentual variation of that measurement This variation was found to be extremely small, below 1 per cent for the majority of the measurements taken Weight represented the most variable measurement Its average percentual variation amounted to 2 58 per cent A separate calculation for those identical twins reared and living in "identical" environments, and for those reared and living in dissimilar environments, showed the average percentual variation in body weight for the first group to be 1 39 per cent and for the second group 3 6 per cent These results, as well as

some others obtained in similar investigations, clearly demonstrate that body weight is determined chiefly by genetic factors but is influenced by environmental factors This latter influence has been found to be far greater in its effect upon body weight than upon other physical measurements Yet it is obvious that under average environmental circumstances the genetic determination of body weight prevails markedly over extrinsic factors, only extreme environmental influences, brought about chiefly by diseases, markedly alter the genetically determined body weight

One of the most interesting facts detected in this field of constitutional physiology and pathology is the amazing similarity of the electrical brain waves, both normal and abnormal, in identical twins [11]

As a matter of fact, psychologic traits also are found to be identical or very similar in identical twins Even criminality of like kind and the tendency to commit crimes of a similar type have been found in identical twins [9]

Interesting psychologic investigations on identical twins have recently been published by Burnham [10] Applying "tests of personality traits," he found remarkable differences in performance, although other psychologic and physical tests gave the expected similarity in the behavior of twins Burnham is reluctant, however, to acknowledge the validity of the applied personality tests

II

CONSTITUTIONAL PATHOLOGY AND ITS GENERAL SIGNIFICANCE

1 What Is Individual Constitution?

A correct definition of the term individual constitution may be derived from the discussion in the preceding chapter It means the sum total of an individual's characteristics as they are potentially determined at the moment of fertilization The individual constitution comprises *all traits induced by the specific constellation of the* individual's genes In genetics the genic composition of the individual is called his *genotype*, as contrasted with his *phenotype*, which represents his actual appearance in physical and psychic structure Both genetic and environmental factors cooperate in the production of the individual's characteristics In genetics the former are called genotypical factors, the latter are called paratypical factors The result of their cooperation is the phenotype of the individual The genotypical factors of the phenotype represent constitution, in other words, constitution denotes the actually realized and patent results of the potential energies represented by the genes According to Stockard,

> Without genetic basis there is no individual, and without suitably arranged complexity of environment the complete genetic basis is unable to produce the normal individual The interaction between the individual and the environment is continuous from the germinal beginning to the end of life, and it is mutual, each modifies and affects the other The individual and the environment are not separate, they are parts of a larger arrangement.

Or, in the words of Jennings

Characters are not inherited at all, what one inherits is certain material that under certain conditions will produce a particular characteristic, if these conditions are not supplied some other characteristic is produced

It seems obvious that these obligatory conditions are provided under average normal circumstances The physical basis of the completed individual psychosomatic personality is the fertilized ovum, with all its tremendous potentialities The environmental conditions for the realization of these potentialities exist in a highly similar degree for all human beings Differences in these conditions account for many modifications but not as a rule for any fundamental alterations of the genotypically determined traits The close similarity between identical twins furnishes evidence that—as Galton expressed it—nature (heredity) plays a far more important role than nurture (environment)

East[12] considers the effect of any ordinary change of environment 'negligible" as compared with the influence of heredity—a statement all the more important in view of the fact that many American scientists, and particularly those in the medical field, are too much inclined to overestimate environmental factors It is delightful to read East's sarcastic criticism of the radical environmentalists and behaviorists *

Such a concept of individual constitution is not generally accepted Many authorities define it as the total biologic make-up of an individual, in other words, they include both the genotypical and paratypical (environmentally induced) characteristics The reasons for preferring our definition of individual constitution, which comprises only the genotype, have been discussed in full detail elsewhere[7] and need not be repeated here One point, however, should be stressed constitution is not a physical entity but a panel and plan of the total set up of the individual personality Constitution com

* East, E. M. Biology in human affairs, pp. 182 ff

prises physical and mental traits, visible and invisible characteristics, which may or may not be detectable by all or any of the various methods of physical examination and laboratory work. Constitution is therefore not a measurable entity, but some of its components may be defined in exact figures.

2 What Is Constitutional Pathology and Its Significance in Medical Practice?

Constitutional pathology is concerned with all problems arising from the abnormal constitution. All structural or functional phenomena encountered in medicine that result from the presence of one or more abnormal genes belong to the realm of constitutional pathology.

a) CONSTITUTIONAL FACTORS IN THE ETIOLOGY OF DISEASES

The first objective of constitutional pathology is the detection of constitutional anomalies that are operative as etiologic factors in disease. There are constitutional defects that are actual diseases, morphologic abnormalities due to pathologic genes, such as cleft palate, certain malformations of the cardiovascular or urogenital tract, congenital dislocation of the hip joint, clubfoot, and many others.

That the great majority of congenital malformations in man are caused by genetic factors is an established fact that does not require any further discussion today.[7, 28, 33] Very few instances of congenital malformations in man can be attributed to extrinsic factors such as serious diseases (e g, virus diseases, particularly German measles), injuries, or X-ray and radium treatment of the pregnant mothers. These congenital malformations are caused by damage to the germ, not by alteration of genes, and are therefore not inheritable. They are comparable to the skeletal abnormalities induced in rats by maternal nutritional deficiency.[34]

To the genetic category *belong those* "*inborn errors of* metabolism"[1] producing an impairment of health by their

direct or remote consequences, such as cystinuria with cystine concretions in the urinary tract, alkaptonuria with subsequent ochronosis and severe osteo-arthritis,[2] or the congenital and hereditary variety of porphyrinuria leading either to a severe type of polyneuritis and ascending paralysis or to the photodermatosis called hydroa aestivale

Some morphologic constitutional abnormalities may not endanger the individual's health unless unusual physiologic circumstances occur, as for instance pregnancy in a chondrodystrophic dwarf Abnormal length or kinking of the large intestine or abnormal attachment of the mesentery may be carried for a lifetime as a harmless and concealed constitutional variation It is conceivable, however, that under particular circumstances such an abnormality may predispose the individual to a volvulus or an intra abdominal hernia A similar situation exists in some cases of "cystic lung" A cystic transformation of a portion of the lung may result from a constitutional, inherited[3] defect of the anatomic structure Such a cystic lung may be a harmless abnormality, it may, however, represent the constitutional predisposition to a spontaneous benign pneumothorax, sometimes occurring repeatedly following an unusual muscular effort or strain

Abnormalities in the region of the central canal may be found casually on microscopic examination of the spinal cord Proliferation of the ependymal cells with cell strands displaced in the central gray substance or congenital hydromyelic dilatation of the canal may represent such constitutional abnormalities, as found by Karplus[4] in members of the same family Although they need not interfere with the health of the individual, they should be considered as predisposing constitutional factors operative in the de[illegible]

I [illegible]

or [illegible]

via [illegible] corpuscles Variable numbers of red cells are produced that exhibit characteristic deformities un

der conditions that do not alter normal red cells This trait is transmitted by heredity as a dominant mendelian characteristic Its carriers may be healthy throughout life If, however, conditions occur that facilitate the sickling phenomenon of erythrocytes in such persons, that is, if local or general anoxemia is brought about by infectious diseases, surgical procedures, or other circumstances that are known to retard the blood circulation, a serious disease may be the consequence of an otherwise inoffensive constitutional deviation Sickle cell disease, characterized by circulatory stasis in the small blood vessels of the inner organs, may develop under such circumstances, with all its consequences, including hemolytic anemia [6] It could be demonstrated that the essential disorder is an engorgement of the capillaries and small arteries in various organs by conglutinated disfigured sickle shaped erythrocytes The abnormal configuration of the red blood corpuscles, enhanced by anoxemia, is the constitutional etiologic factor of sickle cell disease

Another group of diseases developing without any detectable influence of extrinsic etiologic factors results from what Gowers has called *abiotrophy* of certain organs or parts of organs It is the innate degree of perfection, the biologic worth of the anatomic structure of a particular organ, that may be constitutionally diminished as compared with other organs in the same individual or with the same organ in other individuals Gowers conception originally was concerned with certain heredodegenerative diseases of the central nervous system, such as hereditary spinal (Friedreich) and cerebellar (P Marie) ataxia or spastic paraplegia The conception was later extended to other organs, in order to explain the progressive atrophy of the parenchyma, and its replacement by proliferating interstitial tissue, occurring in certain families without evidence of any known extrinsic etiologic factor O Rosenbach[7] spoke of inborn embryonic defects whereby

quite normal functioning resulted in a premature using up of the particular organs *Aufbrauchskrankheiten*, that is, diseases caused by wearing out of organs, was the term applied by Edinger[7] to these ailments Anatomic signs of biologic inferiority and lowered resistance may or may not be present Congenital hypoplasia, structural abnormalities of various kinds, malformations inoffensive in themselves, may be morphologic signs of such a biologic inferiority[7] As a matter of fact, abiotrophy corresponds to a certain extent to a precipitated senile involution[8]

A typical example of the latter is the constitutional precipitation of menopause It is an established fact that the physiologic duration of life, that is, the degree of longevity, is a constitutional trait It varies in different races and families Not all organs and tissues of an individual, however, are subject to senile involution at the same time Some parts of the body may show signs of senility earlier than others and so may bring about a disharmonious senescence of the organism The same holds for the period of evolution There may be a definite disharmony in the development and growth of the various parts of the organism Physiologic senile involution of the ovaries in the white race in temperate climates occurs between the ages of 46 and 50 years In some families, however, the menopause sets in at 40 or earlier The abiotrophic background of such a premature senescence of the ovaries is clearly evident when the constitutional biologic inferiority of the gonads is recognizable from other signs In some of these cases, for instance, the menstrual cycle does not start around the regular age, 14, but at the age of 18 or later I have seen the onset of menopause occur in a woman of 30 after her only pregnancy Her mother had ceased menstruating at 41 and her sister suffered from a marked oligomenorrhea In another *similar case* of precocious menopause the son exhibited a markedly delayed puberty, illustrating the consti

tutional biologic inferiority of the gonads that ran in the family, diminishing but not destroying fertility

Abiotrophy and precipitated senescence are intimately related If we find a senile cataract, deafness due to degeneration of the acoustic nerve, osteo-arthritis, osteoporosis, or advanced arteriosclerosis in a person of 95, these may be considered the normal consequences of old age The same conditions may be present in a person of 50, but here the particular organs involved have suffered an untimely senile involution The practical importance of this knowledge is self-evident Indications of a constitutional biologic inferiority of the affected organ from the past and family history—rather than focal infections, vitamin deficiencies, endocrine disturbances, etc —should be sought in such cases, in order to avoid erroneous interpretations and useless treatments The abiotrophic character of some cases of progressive degeneration of the acoustic nerve can be demonstrated by studying the family history Not infrequently such a degeneration is elicited by exposure to unusually intense acoustic stimuli, for example in artillerymen, braziers, or engine drivers, whose resistance to acoustic stimuli is low as compared with that of the average normal person Premature senile hardness of hearing, and occasionally other degenerative processes in the acoustic apparatus, occurring in members of the same family, may indicate the constitutional biologic inferiority of this particular organ [9]

In the diseases discussed above, the factor of individual constitution represents the actual and practically only etiology, and they are correctly termed constitutional diseases There is a second group of diseases caused solely by extrinsic factors, such as certain bacterial infections, toxemias due to strong poisons, results of severe mechanical injuries, etc In the third and by far largest group of diseases, both constitutional and environmental factors contribute etiologically The role played by each may vary widely This third, large group of diseases covers a wide range between the second group, caused

by extrinsic etiologic factors only, and the first group, originating exclusively on the basis of an inherited constitutional abnormality As a matter of fact, in the majority of diseases there are numerous etiologic factors, some obligatory, others accidental, but all operative in the particular case

If a person has suffered a severe burn, has been poisoned by potassium cyanide, or has been stung by a malaria infected anopheles for the first time in his life, no influence other than this particular extrinsic etiologic factor is needed to bring about the consequent disease If, however, less potent environmental factors come into play, the picture is modified Moderate traumatisms, chronic mild toxemias due to small amounts of poison, tuberculous infection, psychic shock, and many other environmental influences will result in individually different clinical pictures or may produce no actual disease at all Predisposing cooperating factors, both environmental and constitutional, will be decisive in this respect

'Heredity plays a part in the etiology " this statement is to be found in all textbooks of medicine in the discussion of the etiology of many diseases It means that certain inherited, that is, constitutional traits are acting together to bring about the derangement of vital processes characteristic of the disease under discussion In other words, an individual constitutional predisposition is prerequisite to the development of such a disease Diabetes, obesity, gout, essential hypertension, peptic ulcer, cancer, neuroses and psychoses, many infectious diseases such as acute rheumatic fever and tuberculosis—to enumerate but a few—belong to this third group of diseases that cannot become manifest unless the intrinsic constitutional factor plays its part The monograph *Konstitutionelle Disposition zu inneren Krankheiten*, which appeared in 1917 in its first edition,[3] represented the first systematic although tentative effort to detect and evaluate this constitutional predisposing factor in various internal diseases

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vascular disturbances, headache, dizziness, and even retrobulbar optic neuritis It is not only the degree and duration of the poisoning that counts, but also the individual reactions of the various organs to the poison, as well as their different thresholds of resistance, modified both by constitutional and environmental factors

The vitamin research workers of the last few years have taught us to recognize the symptoms and signs of slight nutritional deficiencies, and to associate them with absence or insufficiency of specific vitamins However, it is not only the complexity of the vitamins that deserves our attention, but also the tremendous complexity and variety of individuals It is not possible to attribute every clinical sign to a specific vitamin deficiency[11], the variable reactivity of individuals to such a deficiency must also be considered

What has been said about extrinsic poisons and the lack of essential foodstuff holds true for intrinsic poisons and for deficiencies in essential intrinsic products called *hormones* Individual differences, in part constitutional, account for the variety of clinical pictures in chronic uremia, jaundice, or hepatargia The best illustrations of the general principle in question are furnished by endocrine diseases

The more severe and acute a case of hyperthyroidism, the more typical is its symptomatology and the simpler the diagnosis The milder the intoxication with the thyroid hormone, the more variant is its clinical picture and hence the more difficult the diagnosis

Various symptoms cause a patient with mild hyperthyroidism to consult a physician There may be merely a slightly increased pulse rate or a slight trembling of the fingers accompanied by some nervousness There may be dyspeptic disorders or a mild diarrhea Again, it may be an unexplained loss of weight, a slight glycosuria, or a special tendency to perspiration that brings the patient to the office of a cardiologist, a gastro-enterologist, or a neurologist Only a thorough

b) CONSTITUTIONAL FACTORS MODIFYING CLINICAL PICTURE AND COURSE OF DISEASE

In the early part of the twentieth century, German pioneers in this field (Gottstein, Martius, von Strumpell, and others) proposed a formula to express the proportion of extrinsic and intrinsic etiologic factors in disease

$$D = I/R$$

In this equation, D designates disease, I represents injury in the broadest sense, and R, resistance of the organism to the injury The greater the injury, the less important is the factor of individual resistance in the etiology of the disease If, however, the injury is minor, the individual resistance gains in importance This resistance is inversely proportional to what we call the individual predisposition This predisposition is not a simple entity but the product of various structural and *functional components of the individual, both constitutional* and environmental in nature They determine whether or not a disease may result from the action of an insignificant and slowly acting injurious agent, and they also account for the individual differences in the clinical picture and course of such a disease

The effect of poisons, or the effect of the lack of essential foodstuff, will differ according to the individual predisposition The greater the amount of the poison, or the greater the deficit in essential foodstuff, the more typical will be the symptomatology of the disease The smaller the amount of the poison, or the smaller the degree of nutritional deficiency, the more variant will be the clinical picture and course of the disease The more chronic the action of such an "injury," the more *pronounced will be the individual differences* in the disease Chronic poisoning with lead, for instance, may result in arterial hypertension, arteriosclerosis, anemia, radial palsy, encephalopathy, and gastro-intestinal disorders *in various combinations*, chronic nicotinism may produce dyspeptic disorders, cardio-

In fact, the same mechanism whereby constitutional factors mold the clinical picture and the course of a disease is valid in practically all derangements of vital processes, regardless of what organ is failing, and of whatever may have caused its failure Let us recall the various clinical pictures of arterial hypertension, of coronary insufficiency and thrombosis, or of congestive heart failure Cerebral symptoms, for instance, may or may not come to the fore in these conditions, depending on the constitutional disposition and temperament of the affected person We shall learn in one of the following chapters to what degree constitutional hyperirritability and hypersensitivity of the nervous system, that is, a neuropathic disposition, may mold the clinical picture and course of various diseases such as gallstones, peptic ulcer, essential hypertension, allergic manifestations, and many other pathologic conditions

c) CONSTITUTIONAL FACTORS NECESSITATING MODIFICATION OF ROUTINE TREATMENT

In actual fact, any routine treatment recommended for any particular disease represents no more than a scheme to be adapted to the individual case of the disease This is particularly true as far as the dosage of drugs is concerned Pharmacology supplies the rules for dosage, which is based upon units of body weight But practical therapeutics requires *more* than merely the consideration of body weight The individual peculiarities of a person are often of greater *importance* than the number of pounds he weighs Hence strict adherence [illegible]

[illegible] rigid adherence to pharmacologic rules in attempts at full digitalization of a cardiac, in the effort to prescribe adequate sedation for a severe hyperthyroid case, or in the indiscriminate forcing of fluids in patients with renal impairment[10] Pharmacologic rules result from tests made on a large number of animals or humans

examination, including a carefully interpreted basal metabolism test, can demonstrate the true character of the disease

Some cases of hyperparathyroidism due to a parathyroid adenoma display the classic picture of Recklinghausen's fibrocystic ostitis, while others develop renal concretions or a simple osteoporosis These various reactions spring from the individually different responses to an excess of parathyroid hormone We face a similar situation in hyperinsulinism Its symptomatology runs the gamut from an excessive sensation of hunger, with sweating and abdominal colics, to mental disturbances, palsies, loss of consciousness, and epileptic fits It is not only the degree of hypoglycemia produced by the hyperinsulinism, but also the individual reactivity to this abnormal state, that accounts for the variability of the clinical picture One of my patients with hyperinsulinism had a hypomanic temperament all his life During the hypoglycemic attacks all features of this particular disposition were exaggerated until they culminated in an epileptiform fit

The absence of thyroid hormone produces the classic picture of myxedema A reduced supply of thyroid hormone may result in very diverse clinical pictures, depending on the different thresholds for this hormone existing in various organs—thresholds that must be maintained for normal function This problem will be discussed in greater detail in a later chapter Physiologic or artificial cessation of ovarian function may or may not produce clinical symptoms Every woman experiences her menopause according to her individual constitution This, too, will be described later in more detail

The clinical picture and course of an infection, particularly in the case of a chronic infectious disease, is largely determined by constitutional factors that account, at least in part, for the various localizations of the germs in the body, for the variable defense mechanisms brought into action by the infected organism, and for the variable recuperative power of the organism

and usually valuable treatment of this disease Sometimes the situation may be rather tricky It is known that administration of sulfonamides or of pyramidon may be followed in certain cases by granulocytopenia or agranulocytosis Recently report was made of the cases of two sisters who both developed agranulocytosis at the age of about 16 The condition was discovered in one of the sisters after treatment with sulfapyridine, but the other had not taken this drug before the development of her agranulocytosis[12] The essential etiologic factor in the agranulocytosis in the sisters could not [illegible] mmon constitu[illegible] in a deficient [illegible] granulocytes under certain conditions, with or without sulfapyridine—a drug that in exceptional cases may be injurious to the bone marrow

Many years ago a man of about 45 who had developed agranulocytosis with a septic sore throat was studied in the Policlinic Hospital in Vienna The arsenical stovarsol was administered to the patient and he recovered Today, after about fifteen years, I am inclined to believe that he recovered *in spite of* rather than because of this treatment The man regained complete health and working capacity but his leucocyte count remained constantly at a level of about 4000 In the following years he was twice readmitted to the hospital with a severe bronchopneumonia, and on each occasion had a severe granulocytopenia with a count of about 1500 leucocytes The actual cause of the condition in this case was not a specific germ or a specific drug but a specific constitutional predisposition to exhaustion of the bone marrow in its function of supplying the organism with the necessary amount of granulocytes Such a bone marrow may become exhausted owing either to the strain imposed by a bacterial infection or to the slightly toxic action of certain drugs

It has frequently been observed that the administration of pyramidon (amidopyrine) is followed by agranulocytosis

and are valid for the average, but therapeutists are obliged to treat individuals who frequently do not correspond to the average. Standardization of treatments is based upon scientific foundations and is indispensable for teaching. Nevertheless, intelligent individual modification of recognized standards is an indispensable prerequisite in the art of medicine. A person with serious hyperthyroidism, in a state of great nervous excitement, *must be kept under the influence of sedatives.* But if such a patient, maintained in sleep for several days by large dosage, then succumbs to a pneumonia induced by this treatment and aggravated by his general condition, his death must be attributed to unintelligent application of recognized routine therapy.

The following remark is quoted from a standard textbook of pharmacology, reporting on the subject of the sale of sulfathiazole tablets contaminated with phenobarbital[11] "Untoward responses attributable to the barbiturates are particularly likely to occur in patients with fever, hyperthyroidism, *diabetes mellitus, severe anemia and congestive heart failure.*"

How is this statement to be reconciled with the daily experience that appropriate doses of phenobarbital are an invaluable part of the medical treatment of hyperthyroid patients? The chief stress, in my opinion, should be laid upon the need of adapting the dose to the individual case. In hyperthyroidism particularly there can be no simple standardization of treatment.

The startling results of modern chemotherapy may readily make the physician forget that he should consider not only the germ and the drug but also the patient. It is noteworthy that the administration of less than half of the usual dose of sulfadiazine in pneumococcic pneumonia did not result in a higher mortality or in an increase of serious complications.[12]

It stands to reason that a chance coincidence of a given disease in a patient with a constitutional drug allergy may require the abandonment of an otherwise generally accepted

circulatory stasis in a Negro affected with the sickle cell trait, who needs surgery, have been outlined elsewhere[8]

The decision as to whether or not surgical treatment should be applied in a particular case depends upon the balance between the indications and the contra indications Hardly any other situation in medicine demands as much individualization as this one Correct evaluation of the nervous and psychic components in the clinical picture of a chronic abdominal disease will safeguard the patient s physical and mental welfare, may even save his life Many uncalled for operations have been performed on neurotics of various types Appendectomy, cholecystectomy, gastro-entero-anastomosis, partial resection of the stomach, corrective operations for retroverted uterus, cutting of adhesions, etc , are common surgical therapeutic attempts in such cases Not infrequently, drug addiction is a consequence Tonsillectomy and extraction of presumably infected teeth are recorded in the past histories of such patients These are surgicophilic, psychoneurotic personalities that crave the drama of surgical intervention, and they *cooperate in* achieving the harmful results of such contra indicated surgery

Many years ago, I reported cases of this sort to the Medical Society of Vienna In the discussion, an outstanding Viennese surgeon renowned for h [illegible]

[illegible] it, and this diagnosis and the subsequent surgical treatment are far simpler than is the correct management of such a patient, which will be discussed in a later chapter The fact that chronic appendicitis is a very rare condition, if indeed it ever occurs, was emphasized long ago[7] and was recently again confirmed[10, 11]

Contra indications to surgical treatment also require individualization and consideration of constitutional factors Persons affected with organic valvular lesions of the heart may be better surgical risks than patients with neurocirculatory

There must exist an individual predisposition to such an untoward effect, since it is not encountered in the great majority of persons. Among hundreds of patients who have taken pyramidon in large doses over long periods of time, I have never seen a single case of agranulocytosis. In Eppinger's clinic in Vienna a case of agranulocytosis was purposely treated with pyramidon and recovered nevertheless. Recently, successful sulfathiazole treatment of a patient suffering from agranulocytosis has been reported,[39] although sulfa drugs are known to cause agranulocytosis in exceptional cases. Amidopyrine is an invaluable drug not only as an antineuralgic and a sedative but also because it lowers the capillary permeability and may therefore be used for its antiphlogistic action. It would be regrettable to discard amidopyrine because of its possible although quite exceptional untoward side effects. A similar individualization is necessary when antisyphilitic arsenicals, quinine, sedormid, or certain other drugs are administered, or when intravenous strophanthin therapy is used. Thoughtless standardized routine treatment is unbiologic and may become a menace. Careful individualization is a requirement of biologically sound and successful therapy

Experimental pharmacology and correct prescription writing are prerequisites to good therapeutics, and the knowledge of treatment of diseases is fundamental. The art of treating patients starts beyond the science of pharmacology and therapy. This has been clearly pointed out and excellently discussed by W. R. Houston.[13]

Constitutional factors are also of importance in surgical *treatment*. The indications for an exploratory laparotomy, for the surgical treatment of gallbladder disease, or for a radical procedure in operating on a patient with peptic ulcer, should be influenced by the presence or absence of a carcinomatous tendency in the patient's family. The constitutional sickle cell trait in Negroes calls for careful consideration before surgical treatment is decided upon. Measures to counteract

circulatory stasis in a Negro affected with the sickle cell trait, who needs surgery, have been outlined elsewhere [6]

The decision as to whether or not surgical treatment should be applied in a particular case depends upon the balance between the indications and the contra indications Hardly any other situation in medicine demands as much individualization as this one Correct evaluation of the nervous and psychic components in the clinical picture of a chronic abdominal disease will safeguard the patient's physical and mental welfare, may even save his life Many uncalled for operations have been performed on neurotics of various types Appendectomy, cholecystectomy, gastro-entero-anastomosis, partial resection of the stomach, corrective operations for retroverted uterus, cutting of adhesions, etc, are common surgical therapeutic attempts in such cases Not infrequently, drug addiction is a consequence Tonsillectomy and extraction of presumably infected teeth are recorded in the past histories of such patients These are surgicophilic, psychoneurotic personalities that crave the drama of surgical intervention, and they cooperate in achieving the harmful results of such contra indicated surgery

Many years ago, I reported cases of this sort to the Medical Society of Vienna In the discussion, an outstanding Viennese surgeon, renowned for his wit, put it as follows If a young person undergoes a second laparotomy, the first one was probably superfluous The diagnosis 'chronic appendicitis is very convenient, and this diagnosis and the subsequent surgical treatment are far simpler than is the correct management of such a patient, which will be discussed in a later chapter The fact that chronic appendicitis is a very rare condition, if indeed it ever occurs, was emphasized long ago[7] and was recently again confirmed [15, 17]

Contra indications to surgical treatment also require individualization and consideration of constitutional factors Persons affected with organic valvular lesions of the heart may be better surgical risks than patients with neurocirculatory

asthenia or vegetative stigmatization (von Bergmann), that is, with nothing but a variety of neuropathic constitution chiefly involving the autonomic nervous system.[7] Characteristics of such cases are marked vasomotor hyperirritability, dermographia, lability of the pulse rate and a tendency to orthostatic tachycardia, cold and moist hands and feet, exaggerated axillary perspiration, etc. They are more liable to sudden death due to ventricular fibrillation in the course of a general anesthesia and a surgical procedure than are many patients with organic heart diseases. It has recently been emphasized[16] that persons with mitral stenosis may reach old age without clinical symptoms and without any impairment of their physical fitness. I knew a woman who was aware of her heart disease for fifty years and recovered from a bronchopneumonia at the age of 76. Age, nutritional condition, blood pressure, the status of the nervous system, heredity—briefly, the entire psychosomatic personality—must be considered in weighing the indications and contra-indications for surgery.

For a proper evaluation of the great importance of psychotherapy in disease, it is well to review the results of placebo therapy published by various authors in the past few years. Cardiac clinics in London and New York City each treated a large group of angina pectoris patients with the various drugs usually prescribed for this disease. Another group was treated only with placebos, and it was this group that showed the best therapeutic results.[17,18]

A similar experiment was tried with persons suffering from arterial hypertension,[19] and recently with a group of 32 cases of hay fever due to ragweed pollinosis.[20] The latter were treated with a placebo and compared with a similar group treated by means of oral pollen therapy. The placebo consisted of capsules identically colored but containing no pollen extract, and was administered together with injections of physiologic saline solution. In the first group, 7 of the cases were improved, and 2 markedly so—"an apparently better

result than that obtained from any of the patients receiving oral pollen therapy"[20]

It is not suggested that placebo treatment replace routine therapy for angina pectoris, arterial hypertension, or pollen allergy The experienced physician, however, knows what [illegible] to pharmacologic treatment He will evaluate the relative importance of the psychologic factor in the pathogenesis of a disease in different individuals

Hyperthyroidism, ill defined abdominal complaints, unusual abundance of disparate symptoms require such a study in the first place The need for some kind of adjuvant psychotherapy is to be inferred chiefly from constitutional factors in the individual, apart from the illness Capacity to recognize this demand and to adapt the routine treatment of an illness to the individual characterizes the good therapeutist The choice of the most suitable psychotherapeutic method will be the subject of a later chapter

Scientific interest concerning the management of the menopausal syndrome is concentrated today chiefly upon the determination of the right dosage and the best method of application of estrogenic hormone This treatment seems to be entirely justified, since there is no doubt that lack of ovarian hormone is the essential causal factor in the menopausal syndrome There are now available powerful preparations of estrogenic hormones that can entirely rectify the hormonal imbalance of the menopausal syndrome But the results of this treatment are not always satisfactory, as they should be if hormonal imbalance were the only cause of the syndrome. In fact, the hormonal assay after treatment may show a perfect readjustment to the normal level, yet the clinical symptoms may remain unchanged The incongruity between the hormonal assay and the subjective condition of the patient has been emphasized by many experienced endocrinologists [21,22]

How can we account for the fact that in many cases of menopausal syndrome, satisfactory results were obtained over a long period before the ovarian tablets administered contained any appreciable amount of the potent hormone? The therapeutic problem here is evidently not only an endocrine one, but one involving the whole personality. It has recently been shown that an increased amount of gonadotropic hormone appears in the urine as early as three days after ovarectomy.[22] From an academic point of view, Walter, Geist, and Salmon[23] seem to be justified in suggesting early hormonal therapy, even preceding the ovarectomy. It is doubtful, however, whether this procedure will ensure more satisfactory results in practice. A therapeutic success is occasionally obtained with sedatives where hormonal therapy has completely failed. Yet bromides, phenobarbital, or calcium should certainly not replace estrogenic hormone in the routine treatment of the menopausal syndrome. Both estrogens and sedatives have their place in securing the appropriate readjustment of the psychosomatic state, that is, of the whole personality of the patient.

d) SIGNS OF CONSTITUTIONAL DEVIATION AND SIGNS OF DISEASE

Sir Thomas Lewis[24] has written significantly as follows: "Medical men are insufficiently conversant with what constitutes normality, or the range of normality, in the human being. They regard as pathological many phenomena which are in reality not only compatible with health, but are actually physiological. It is of much consequence that this argument should be brought home."

The problem of normality has been dealt with previously. Establishing a dividing line between the normal and the abnormal is obviously desirable. But in addition one should be familiar with those *morphologic and functional signs that* may be indicative of an actual disease but may just as well represent the harmless stigmata of a deviation of the individual

constitution Abnormalities in the quantity and distribution of hair, for instance, or certain disproportions of the skeleton, are not necessarily due to an endocrine disease but are often due to constitutional traits running in a family The same may hold true of marked lymphocytosis, eosinophilia, brady cardia, arterial hypotension, renal glycosuria, gastric achlor hydria, pseudo Babinski sign, nystagmus, etc

The pseudo Babinski sign, for instance, is a rather quick dorsal extension of the big toe associated with a dorsal exten sion of some or all other toes on stroking of the plantar surface It is usually not elicited constantly in the same person This phenomenon was described by the author in 1917 as an occa sional occurrence without any clinical significance but often associated with other signs of constitutional deviation It is, in my opinion, due to the abnormal persistence of an evolu tionary state of early childhood that under normal conditions is only temporary—i e , that phase of life in which the physio logic Babinski reflex is succeeded by the normal plantar reflex The pseudo-Babinski is therefore considered one of the many signs of a partial infantilism, that is, of an abnormal persistence of a normally transient stage of evolution It is easy to see that such a constitutional deviation may be a mis-leading sign if taken as indication of a pyramidal tract lesion Similar errors may be caused by the more or less intense lateral or vertical nystagmus occurring as a constitutional sign of a poorly balanced contraction of the eye muscles Systematic studies on Negroes, carried out in collaboration with Dr Charles Midlo in New Orleans, showed relatively high frequency of both the pseudo Babinski sign and nystagmus in the Negro population

Recently it was emphasized by Yakovlev[11] that muscular exertion and fatigue may cause Babinski s sign to appear in a certain group of otherwise healthy people without any struc tural damage of the corticospinal tract In the constitu tionally inferior individuals it develops after a relatively small

amount of exertion, insufficient to cause its appearance in normal people" The author proposes to use the "exertion Babinski" as a test of endurance, indicating "a constitutional weakness or fragility of the nervous system" As a matter of fact it was found more readily and more frequently in a group of imbeciles and psychotic individuals than among healthy college graduates There is obviously no major difference between the pseudo-Babinski and this exertion Babinski, as far as its nature and significance are concerned

e) GENETICS AS A PART OF CONSTITUTIONAL PATHOLOGY

Since constitutional pathology is concerned with all pathologic phenomena arising from the action of one or more abnormal genes, it stands to reason that genetics is an essential part of this branch of medical science Genetics supplies us with knowledge about genes, their nature and activity, the laws of their transmission throughout generations, and their structural basis in the chromosomes

The problems of human genetics, however, are not exhausted by stating what morphologic or functional characteristics of the organism may be inherited and what type of inheritance they may show, whether dominant, recessive, sex-linked, etc The chief problem lies in the recognition and complete isolation of what we call mendelian units or genes It is necessary to reduce the phenotype, that is, the actual appearance of an individual, to its genotypical basis, and to unravel as far as possible the intricate complex of genes However, one must realize that the potential energies represented by the genes do not always correspond to simple morphologic or functional characteristics perceptible in the human being They represent categories of their own Genes for definite stature and body proportions, for the amount and distribution of fat tissue accumulated, for the hair pigment, for the shape of the nose or the pinnae, for metabolic functions, for psychic features, for the speed of evolution and maturation, as well as for the wear

and tear of various organs, for the reactivity to certain infections—and for all the manifold constitutional traits—are gathered in a double set in the chromosomes of the fertilized ovum This of course has not the slightest resemblance to the actual appearance of an individual

The relation of the phenotype to the sum total of the genes, [illegible]

making up the whole organization of the future factory This analogy may be maintained further Just as one special detail of the whole plan—it may be architectural, mercantile, or anything else—is entirely without significance by itself if separated from the whole plan, so a gene or a complex of genes separated from the sum total of the genotype becomes senseless and means nothing Only as a part of the genotype and in close cooperation with all other genes does any one represent powerful potential energy

From the science of genetics we learn that on the one hand different genes may produce indistinguishable phenotypical effects, while on the other hand single genes may extend their activity to several quite different parts and functions of the body To designate this latter fact the term *pleiotropism* of genes is used by geneticists In tuberous sclerosis (or epiloia) the combination of nodular neuroglial proliferation in the brain, adenoma sebaceum on the face, tumor formation, especially in the heart and kidneys, mental deficiency, and epilepsy, may arise all from the action of one abnormal gene [33] Another example of pleiotropism is the condition known as phenylpyruvic oligophrenia, that is, a hereditary combination of mental deficiency with a metabolic disorder in which phenylpyruvic acid is excreted in the urine [33] [34] In this connection attention may be drawn to the well known statements of Kretschmer concerning the relationship between body build and psychic temperament and morbidity The frequent

association of the lateral (pyknic) physical type with cycloid temperament, and of the longitudinal (asthenic) physical type with schizoid personality is, in my opinion, due to pleiotropism of genes

We must bear in mind that one particular gene need not always produce the same result This depends both upon the different backgrounds furnished by other genes and upon different environmental conditions

Sex-linked traits such as hemophilia or total color blindness are well known Their genes are situated in the sex chromosome

Linkage of genes is the scientific term for location of genes in the same chromosome Hence these genes may frequently have the same destiny They have a chance to be exposed together to the same influence that elicits an alteration of the genes, called mutation, and they are as a rule transmitted to the offspring in combination with one another There is ample evidence that many clinical occurrences are best interpreted as the result of genes carried in one chromosome pair The combination of polydactyly and syndactyly, or the strange association of a hereditary deficiency of the patella with a hereditary aplasia or hypoplasia of the thumbnails, has been explained as due to a linkage of genes [36] The typical hereditary complex of obesity, hypogenitalism, mental deficiency, retinitis pigmentosa, and polydactyly, known as the Laurence-Moon-Bardet-Biedl syndrome, is also an example of linkage of genes This concept, first expressed by Aschner[38] and Bauer,[39] has recently been confirmed by Sorsby, Avery, and Cockayne [30] We shall refer to this syndrome later

Another instance of the genotypical relationship of several different pathologic states is the syndrome of fragility of the bones, blue sclerae, and hardness of hearing that occurs in certain families as a hereditary condition Each of the three states composing the complete syndrome may occur alone without the other hereditary characteristics [40] The hardness

of hearing is in most cases due to otosclerosis but in others to a labyrinthine acoustic atrophy. Otosclerosis is an affection of mesodermal tissue, labyrinthine acoustic atrophy is an affection of ectodermal tissue. But both of them have been shown to be due to the same hereditary deficiency, to the same pathologic genes[9] The alternation of the two in the typical syndrome comprising abnormal fragility of the bones and abnormally thin and therefore blue sclerae is important proof of this statement. There can be but little doubt that the syndrome under discussion is produced by several pathologic genes related to one another, probably by the fact that they are located in the same chromosome and are therefore frequently affected together in the same individual and transmitted in combination to the offspring[11, 13, 14]

The neutrophilic leucocytes of a normal individual show no segmentation of the nucleus, or only two segments, at a rate of about 25 per cent, whereas 75 per cent have more than two segments. There is a constitutional variation of the neutrophilic leucocytes in otherwise healthy persons in which there are very few white cells with three segments and practically all white cells have a nonsegmented or only bisegmented nucleus. This harmless variation is known as *Pelger's anomaly*. It is transmitted by heredity as a dominant mendelian factor. It is clinically important only because it may readily be mistaken for an excessive "shift to the left" and therefore be diagnostically misleading. Pelger's anomaly, however, is of great biologic interest, because it seems that it is incompatible with life if it is inherited from both parents. In the terminology of genetics. In homozygotic state it is a lethal factor. Nachtsheim studied Pelger's anomaly in rabbits, it occurs in these animals as well as in humans. He bred a strain of rabbits transmitting this anomaly as a dominant characteristic. In homozygotic animals all leucocytes had a round and pyknotic nucleus, the animals showed retarded development, shortened and curved long bones, and diminished vitality, and

died at an early age These facts demonstrate how far reaching systemic consequences may arise from one abnormal gene that is harmless if it occurs single and if it is checked by its normal though recessive allelomorph, but that becomes deleterious and even fatal if it occurs double and unchecked [41]

Peculiar inclusions in the neutrophilic leucocytes of a Cuban man and of all his thirteen children have recently been described by Béguez César [42] Four of these children had albinism, nystagmus, granulocytopenia, and lymphomonocytosis They died of a malignant agranulocytosis resulting in "complete failure of all medullary functions" These are the facts, the interpretation of them is far from being clear This instance is, however, an illustration of how an abnormal genetic factor may under certain circumstances become operative in causing a serious disease

In this book we shall deal with rather intricate problems occurring in the analysis of diseases with a constitutional background A background of genetics will be needed to achieve a sufficient understanding of the situation For those, however, who see human genetics merely as deciding whether a particular anomaly is transmitted as a dominant, recessive, or sex linked characteristic, or whether it is due to one or more abnormal genes, it might be well to emphasize with Fraser Roberts[25] that it is impossible to settle once and for all the mode of a trait and thereafter to apply that knowledge to each new case that presents itself

III

CONSTITUTIONAL BIOLOGIC INFERIORITY OF ORGANS AND TISSUES

Clinical and laboratory experience has proved that damage of an organ brought about by trauma, through infections, or otherwise, may mark this particular organ as a locus minoris resistentiae temporarily or forever. Such a *locus minoris resistentiae* may determine the localization of streptococci and other bacteria that have entered the blood stream spontaneously or have been injected experimentally. Not infrequently this principle accounts for the localization of tuberculosis in a particular bone or joint. Tumors may develop in organs predisposed by previous injuries. Even metastases of tumors may be favored by such loci minoris resistentiae. My former associate, C. V. Medvei, reported a case of hypernephroma with metastases in the skeleton, limited to two parts of it that obviously had become loci minoris resistentiae through previous severe gout attacks.[1] Such a susceptibility to various pathologic processes may rightfully be termed biologic inferiority.

As was pointed out in the previous chapter, the biologic worth of a particular anatomic structure may also be diminished by a *constitutional* defect. Diseases arising from such a constitutional biologic inferiority are themselves the only reliable evidence of its existence, no matter whether or not such a constitutional *biologic inferiority* is detectable before the onset of the disease by morphologic signs or by chemical or

other tests Intelligent study of diseases from the genetic standpoint is therefore the only method of detecting the constitutional biologic inferiority The results of such a study, however, are just as cogent as conclusions drawn from laboratory experiments Nature supplies us with spontaneous *experiments on human beings, furnishing far more amazing* results than can ever be obtained from laboratory experiments carried out by human workers It is up to us to comprehend and to analyze properly what nature provides

1 Bones and Joints

In 1914 an interesting family history was reported in the *Journal of the American Medical Association* by Ransohoff[2] A 68-year-old woman dies of a sarcoma of the femur Her younger son dies of the same disease at 48 The elder son develops a generalized severe case of Paget's disease (osteitis deformans) at 50 that eventually prevents him from walking His daughter at the age of 6 months suffers a spontaneous fracture of the tibia that shows no tendency to heal Later the fibula is found to be fractured as well When the child is 13, the leg is more than 3 inches shorter than the other, and when she is 16 the leg has to be amputated on account of severe pain and trophic changes The author is inclined to assume imperfect osteogenesis as the cause of the puzzling condition and concludes his report as follows

> I am safe in saying that in all these cases bone tissue was by heredity a locus minoris resistentiae, a phrase little used during the last decades, in which the bacteriologists pushed aside our theories of the causes of disease But for many things we are forced to fall back on heredity

In the family studied by Ransohoff, Paget's osteitis deformans and bone sarcoma occurred in different members of the stock It is not uncommon to see bone sarcoma developing in a patient with Paget's disease of long standing Several cases of this kind were recently reported in this country Years ago I was consulted by a 67-year-old Frenchwoman

with far advanced osteitis deformans, involving the skull and lower limbs, whose brother's son was suffering from multiple cartilaginous exostoses One of her sisters died from multiple osseous metastases of a breast cancer That Paget's disease may befall several members of a family has been emphasized by many clinicians[5] Three cases of bone sarcoma have been reported in patients with "polyostotic fibrous dysplasia"[49] Considering the infrequency of this congenital disorder of bone development, its combination with bone sarcoma can hardly be a casual coincidence All these facts tend to indicate that a constitutional biologic inferiority of the bone system is the predisposing basis of Paget's disease, bone sarcoma, and various other diseases of the skeleton

That *acute rheumatic polyarthritis* frequently occurs in several members of the same family has been known for a long time[6] Extensive studies of M G Wilson et al[42] lead to the conclusion that the most important factor in the etiology of rheumatic fever is the genetic susceptibility of the host The statistical figures of the authors were consistent with the hereditary mechanism of a single autosomal (i e , localized in one of the non-sex chromosomes) recessive gene In Widal's clinic in Paris I saw a case of severe arthritis caused by Eberth's typhoid bacillus The joints of the patient had been affected by acute rheumatic polyarthritis some years before

The combination of psoriasis with a chronic deformative polyarthritis is a not uncommon occurrence One group of authors advocated the theory that a special germ is the cause of this syndrome affecting both the skin and the joints An other group believed in a common metabolic disturbance In collaboration with my assistant, Dr Vogl, I was able to show that in certain families with such a *polyarthritis psoriatica*, some members were suffering from psoriasis only, others from a chronic polyarthritis only, and some presented the combined syndrome[3] Furthermore, we were able to show that different types of joint diseases are to be found in patients suffering

from psoriasis In general it is the chronic inflammatory type but occasionally chronic degenerative arthrosis occurs In one instance it was an angioneurotic hydrops intermittens of the joints that was found associated with psoriasis in several members of the family, *one of them presenting in addition an* inflammatory deformative arthritis.

The pedigree and abridged history of this family are pertinent here (fig 1). Three members were personally examined

Patient *II* 1 was a 30-year-old woman suffering from periodically recurrent and painful swelling of the right knee joint. The swelling appeared every seventh day and lasted about forty-eight hours It had occurred for the first time ten years before. For eight months past the left knee joint had been

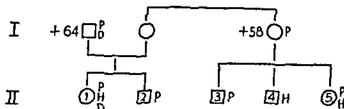


FIGURE 1

P = psoriasis D = diabetes mellitus H = hydrops articulorum intermittens

affected in the same manner It would become swollen three days after the right one No treatment had proved effective

For a year the patient had been suffering from stinging and burning pain in the neck, right shoulder, and both hips Partial stiffening of the hip and knee joints had gradually developed, independent of the intermittent swelling of the knees Psoriasis had been present since childhood Diabetes mellitus had been discovered four years before For the last seven years [illegible]

Physical examination revealed a thin and rather pale woman with impaired mobility of the neck, jaw, right shoulder, and hip *Passive and* active movements of these joints were painful The right leg was rotated externally. The right knee was moderately swollen, tender, and fluctuation was elicited Its mobility was impaired The left knee was not swollen at the time of the examination but was tender and not quite freely movable.

Psoriasis was found at the elbows, the head, the pinnae, and the fingernails. Glycosuria was present. The blood sugar level was 190 mg per 100 cc. of blood. X rays showed bone atrophy around the knee and hip joints, thickening of the capsule and narrowing of the articular spaces in the hip joints. The latter was also found in the intervertebral joints of the cervical spine. Physical examination did not reveal other abnormalities The blood count was normal

The case was diagnosed as a combination of hydrops articulorum intermittens with chronic inflammatory polyarthritis, psoriasis, diabetes mellitus, and ovarian insufficiency.

Patient II 4, a cousin of the first patient, was a man of 26 At the age of 5 he was treated for a swelling of the left knee joint. At the age of 10 he was kept in bed for five weeks because of fever and a swelling of the left ankle. From his sixteenth to his nineteenth year the patient suffered from an inten- [illegible] three days duration. There was no rise of temperature During the period of swelling the patient was able to walk, although with difficulty and pain. Psychic disturbance and alcohol increased the severity of the swelling, but the rhythm of its appearance was not altered. Physical examination in the free interval gave completely negative findings except for some "degenerative stigmata" (p. 157) such as hypoplastic jaw, arched palate, and absence of the pharyngeal reflex.

This patient represented the uncomplicated picture of hydrops articulorum intermittens

His sister (II 5) was 24 years of age. She also showed the typical picture of intermittent hydrops articulorum For six months she suffered from a painful swelling of the ankles, occurring alternately on either side every *twelfth* day When the swelling of one ankle cleared up after three days, the other ankle began to swell. In this patient the periodic swelling was observed several times. Patches of psoriasis were present behind the pinnae. Physical examination gave negative findings except for an arched palate, increased vasomotor irritability, moist, cold hands, an unstable pulse rate, and exaggerated deep reflexes. The first swelling of the ankle occurred after defloration of the patient, which had been difficult and associated with severe psychic shock.

The only thing we know about the etiology of psoriasis is its hereditary occurrence That all kinds of polyarthritis are frequently found in several members of a family is well known to experienced physicians An observation published by Marinesco and Allende[4] illustrates this fact in a particularly instructive way Two brothers and one sister all developed in the first years of their childhood a deformative type of infectious chronic polyarthritis There is no doubt that the joints were a constitutionally weak point in this family and were therefore highly disposed to bacterial infections Thus the psoriatic arthritis should be interpreted as a manifestation of a combined abnormality of two genes, one accounting for the psoriasis, the other for the constitutional predisposition of the joints to various types of diseases Whether or not a linkage of these two genes must be assumed is open to discussion

Intermittent hydarthrosis (hydrops articulorum intermittens) alone may occur in several members of a family I had under my care a 56 year-old woman who had been suffering for thirty years from intermittent swelling of either the right or left or both knees, occurring every eleventh day In the last six months the right wrist and right elbow had participated in the swelling One brother, a sister, and a first cousin suffered from the same disease for years The swelling occurred in a regular rhythm, at intervals of from eleven to thirteen days There was bronchial asthma in several members of the family

2 Kidneys

There are many reports, chiefly in the older literature, on the occurrence of acute or chronic nephritis in several members of a family[5] In a family reported by Eichhorst, the grand mother, mother, her two sons, and one daughter suffered from chronic nephritis The Dutch clinician Pel reported a family comprising 18 cases of chronic nephritis in three generations It is particularly noteworthy that a child of this stock developed

acute nephritis during an attack of chickenpox, which is quite an unusual complication I had under my care a physician of about 35 who developed a severe acute hemorrhagic nephritis after a streptococcic tonsillitis His sister and mother had died of chronic nephritis with subsequent uremia Scarlet fever regularly affects the kidneys in certain families and not in others Eichhorst observed 3 cases of nephritis among four children of a family, all of them suffering from impetigo contagiosa One of these children died of uremia Volhard mentions two brothers with acute hemorrhagic nephritis admitted to the hospital at the same time Causal factors were a tonsillitis in one, a staphylococcic infection of the leg in the other Observations of this kind induced Castaigne and Rathery[6] to use the term *débilité rénale congénitale*, that is, congenital weakness of the kidneys We may rightly call it constitutional biologic inferiority of the kidneys

It is interesting that in some cases such a constitutional renal "weakness" may be indicated by a functional anomaly Postural, orthostatic, lordotic, cyclic, or intermittent albuminuria are the terms designating such a benign functional anomaly of the kidneys It would lead us far afield to discuss the pathogenic mechanisms involved in the production of temporarily increased permeability of the renal filter What matters here are two facts

First, there are severe strains and conditions potentially injurious to the kidneys, such as a very cold bath or extreme physical exercise, that provoke temporary albuminuria in practically all individuals The less extreme the noxious influences are, the smaller is the likelihood of a response to them with albuminuria The functional resistence of renal parenchyma obviously shows individual differences Exceptionally, even mental strain, psychic emotions, rich meals, masturbation, and other factors may provoke transitory albuminuria The second fact of interest in this connection is the occurrence in several members of a family of benign "func-

tional" albuminuria, and of *both functional albuminuria and* nephritis in different individuals of the same stock[8]

Two instances of constitutional biologic inferiority of the kidneys may serve as illustration

A 25 year-old Filipino girl, a music student in Vienna, had small amounts of albumin constantly in her urine, with occasional red cells and granular casts in the sediment There was no indication of functional insufficiency of the kidneys, blood pressure and blood nonprotein nitrogen were normal The patient's father and three of his brothers had died of nephritis, as well as their father and the latter s sister

A 15 year-old boy developed acute glomerulonephritis with measles The albuminuria disappeared completely after several weeks Five months after the illness, the nephritis recurred after exposure to a rainstorm There was constant albuminuria, with casts and red cells in the sediment After five weeks the urine was found to be entirely normal Once the boy again temporarily showed heavy albuminuria when his blood was taken from the cubital vein for chemical tests The procedure induced almost a fainting spell in the nervous and vasolabile patient Needless to say, blood chemistry, blood pressure, and renal function tests gave normal values After another cold the boy developed an orthostatic type of albuminuria The patient s father had albuminuria up to his eighteenth year The father s sister was suffering from nephritis Two brothers of the father s mother were suffering from renal concretions

Recently 2 cases of congenital absence of one kidney in the same family have been reported[41]

3 Heart and Blood Vessels

The heart or the blood vessels may also be sites of constitutional biologic inferiority[8] The accumulation of cases of endocarditis in certain families is a hint in this direction, the frequent combination of congenital malformations of the heart and of the large arteries with acquired endocarditis of rheumatic or other bacterial origin proves it

Among 34,023 autopsies studied by Gelfman and Levine,[42] 453 cases (1 3 per cent) of congenital heart defect were found, 181 of these individuals had survived at least two years Of

these patients surviving over two years, 16 5 per cent had acute or subacute bacterial endocarditis, 14 per cent had a complication of rheumatic infection With regard to the special type of congenital heart defect, the incidence of bacterial endocarditis was found to be as follows in 42 per cent of all cases and in 57 per cent of the uncomplicated cases surviving over two years with interventricular septal defect, bacterial endocarditis occurred, in 28 6 per cent of all cases and in 20 per cent of the uncomplicated cases surviving over two years with patent ductus arteriosus, bacterial endocarditis was present, in 12 5 per cent of all cases of Fallot s tetralogy and in 29 per cent of those surviving over two years, bacterial endocarditis was found

The original conception was that bacteria circulating in the blood stream attach readily to the abnormal edges, brims, and niches present in a congenitally malformed heart This theory, although correct, is not sufficient to explain the whole available material pertaining to our problem It is for instance *not* consistent in application to a malignant endocarditis localized at the pulmonary valves and *combined with* a septum defect in a 21 year-old man,[7] or to a case of mitral stenosis in a 5½-year-old child with congenital atresia of the isthmus aortae[8] Fifty out of 100 cases of congenital interauricular septum defect are reported to have been affected with acquired mitral stenosis[9] Furthermore, families have been instanced in which several members had rheumatic heart or otherwise acquired valvular disease, others having congenital heart disease In four generations of a family described by Rezek,[10] 2 cases of congenital heart disease were encountered among 8 cardiac patients Foggie[11] reports a case of dextrocardia occurring in a family with an extraordinary accumulation of heart disease He concludes "The present case, with its three generations of heart disease, would thus seem in its displacement and defect to indicate a weakening in the germinal area concerned in the development of the heart" Hence the

aforementioned mechanical theory does not entirely cover the facts Genetically determined biologic inferiority, with subsequently diminished resistance, is a better description Nevertheless, mechanical factors created by congenital malformations may be paramount in so far as they may determine the localization of a bacterial endocarditis or endarteritis

Correct comprehension of this situation is all the more important today, since it touches on one of the most spectacular achievements of modern surgery The rationale of ligation of a patent ductus Botalli inheres in removal of the abnormal communication because of its disturbance of the mechanics of blood circulation on the one hand, and prevention or cure of a Streptococcus viridans invasion, frequently occurring at this very spot, on the other To date, several cases of S viridans endarteritis localized in the patent ductus seem to have been cured by the operation [12,55] This result alone justifies the rationale so far as its second part is concerned A situation as simple as this is rare *Ligation of the patent ductus Botalli*, so successfully inaugurated by R E Gross,[13] can remove only the mechanical part of individual predisposition to bacterial invasion of the heart and neighboring vessels, but the biologic inferiority remains unchanged The future will determine to what extent such biologic inferiority is prepotent Will the surgically treated individuals with patent ductus escape the fate of subacute bacterial endocarditis menacing about 30 per cent of them?[14,43]

That the mechanical factor of such a predisposition to endocarditis may be dispensed with, is best illustrated by an observation of Strebel and Steiger [15] Seven out of eight children in a family were suffering from displaced lens due to aplasia of the suspensory ligament Their mother was afflicted with the same eye defect In the next three generations almost all siblings, in addition to manifesting the same anomaly, developed rheumatic endocarditis with subsequent valvular lesions The genetic basis for such a marked familial predis

position to endocarditis was merely a constitutional biologic inferiority of the heart, not detectable by any signs before the [illegible]

Another genetic deviation, the [illegible] tion of the fingers known as arachnodactyly (Marfan), is frequently associated with congenital or acquired (*rheumatic*) heart disease In one such case recently reported,[52] a dislocated lens was found as an additional degenerative stigma in a 21 year-old youth, who died of dissecting aneurysm of the aorta

Congenital hypoplasia of the aorta as a predisposing factor *in dissecting aneurysm in young individuals has occasionally* been recorded since Virchow's time[5] Systematic studies[53] have shown a surprisingly high incidence of congenital narrowing of the aorta, varying in degree up to extreme stenosis, and coarctation This was found to occur in 31 9 per cent of the 141 cases" of dissecting aneurysm in young persons

Most interesting is the fact that alterations of the heart action, such as paroxysmal tachycardia, may occur as a hereditary trait In a family reported by Leusser[54] there were 6 cases of paroxysmal tachycardia in three generations Oehnell[55] studied two similar families Numerous members of these families suffered from paroxysmal tachycardia or other abnormalities of the heart rhythm Even auricular fibrillation was observed as a familial trait[56]

In a later chapter we shall refer to constitutional biologic inferiority of the heart as the determining factor in the localization of neurotic and psychoneurotic symptoms It may also determine the earliest and chief complaint of the hyperthyroid patient

It is known that not only arteriosclerosis but even its localization in a particular branch of the arterial system may represent a familial trait I have seen three brothers all die suddenly

of coronary thrombosis at the age of 50. Cerebral accidents may sometimes terminate the lives of most of the members of a single family. It does not matter here whether such accidents are due to cerebral arteriosclerosis, to essential hypertension, or to what French authors called *diathèse anévrismatique généralisée*. The localization of the vascular process is what matters, hinting as it does at the constitutional biologic inferiority of this particular branch of the vascular system.

The cooperation of a constitutional biologic inferiority of the veins in the production of varicosities becomes obvious if extensive varicosities are encountered in otherwise healthy young persons, particularly males. Evident heredity in such cases is not uncommon.

4. Respiratory Tract

The occurrence of chronic bronchitis in several members of the same stock induced French authors to speak of a *débilité bronchique*. That the larynx is an Achilles' heel in certain families can hardly be denied when we learn that identical twins developed a laryngeal papilloma at the same time,[16] or that repeated edema of the glottis eventually proved fatal to five out of nine members of a family.[17]

A peculiar observation pointing to a constitutional morbid predisposition of the respiratory tract was first made by Kartagener.[18] Bronchiectasis is occasionally found to be associated with congenital absence of frontal sinuses. This combination was recently encountered in identical twins in the Mayo Clinic.[19] Although bronchiectasis is an acquired disease, some individuals may have congenitally weak bronchial walls, thus predisposed to future dilatation. It has been argued that the type of bronchiectasis under discussion may represent a particular variety, different from the usual cases of this disease, and closely related to congenital cystic disease

of the lung[19] The constitutional character of the latter has been emphasized previously

5 Nervous System

Regarding the nervous system or special parts of it as constitutional loci minoris resistentiae, I wish to mention but a few of the many clinical experiences that point to this[6] So-called rheumatic facial paralysis (Bell's palsy) has occasionally been observed in several persons belonging to the same stock, some of them having been affected repeatedly Mendel[10] reported a father and his two sons as having suffered from a radial palsy resulting from different and what would ordinarily be [illegible] Concerning the fasci- [illegible] eurofibromatosis, Gard- [illegible] nprising 217 persons in five generations, thirty-eight of whom suffered from deafness of both ears In 7 of these cases the clinical diagnosis was that of bilateral neurofibroma of the acoustic nerve, in 2 of them this diagnosis was confirmed by autopsy *Neurofibromatosis* illustrating constitutional biologic inferiority of an organ as an auxiliary causal factor in the development of tumors, will be referred to in a later chapter

The hereditary occurrence of tuberous sclerosis,[3, 16] syringomyelia,[3, 17] Pick's disease,[18] and many other conditions has been known for a long time

Electro-encephalography has largely contributed to our conception of the etiology of epilepsy Abnormal electrical brain waves were found not only in epileptic individuals but also in many of their relatives Such a "cerebral dysrhythmia" has been rightfully interpreted as a sign of constitutional predisposition to epilepsy[19] This predisposition "lies dormant until activated by injury or serious disturbance of the brain [environment] Both spark and gunpowder are required for the explosion of a fit" (Lennox)[19] I would not hesitate to add·

The greater the constitutional predisposition, the lesser the necessary environmental factor; its importance may even become negligible[5] No wonder that such an epileptic predisposition was found (by electro-encephalography) to be present in individuals who had had "anesthetic convulsions" during a previous operation[60]

It is common knowledge that different varieties of constitutional organic and functional diseases of the central nervous system may be encountered in certain families At a time when alcoholism of a severe type in women was a great rarity in Vienna, I had under my care a 45-year-old woman of high social standing She had lost her moral resistance through alcohol addiction to such an extent that she was indicted for stealing in order to secure the large amounts of alcoholic beverages she wanted Her brother, living in a distant place in Europe, was also a severe addict Her sister was a psychopathic crank The mother died at 60 of a brain tumor The mother's mother was an illegitimate child, a fact pointing in those days, and in their social sphere, to an unusual lack of moral inhibitions *Careful family studies of adult patients afflicted with some kind of tuberculosis of the central nervous system, including tuberculous meningitis, revealed a particular* frequency of various kinds of severe cerebral disease in such families[22]

6 Eyes

Oculists are familiar with the fact that persons with different coloring in the two irises (heterochromia of the iris) are predisposed to iridocyclitis affecting the lighter eye This part of the eye may be a *constitutional locus minoris resistentiae* without any manifestation preceding the disease A 48-year-old woman under my observation developed an insidious chronic iridocyclitis of the left eye at the onset of her menopause Outstanding oculists were unable to detect the etiology Two out of the patient's six brothers and sisters

were suffering from the same condition of the left eye E Fuchs[4] reports the cases of three siblings, two of whom succumbed to retinal glioma in their early childhood, the third exhibiting coloboma of both the iris and the choroid, indicating the constitutional biologic inferiority of the eye

7 Ears

Experienced otologists[23] know that in certain families all kinds of ear diseases are to be encountered, such as otosclerosis, hereditary acoustic degeneration, deaf mutism, and sometimes malignant suppurations of the middle ear I used to say that otologists make their living on certain families, while other families never require an otologist's attention Extensive studies carried out in collaboration with C Stein,[24] on a large number of families affected with otosclerosis and with hereditary degenerative atrophy of the acoustic nerve, led to the conclusion that there is an intimate genetic relationship between varieties of impairment of hearing, including hereditary congenital deaf mutism We felt that all available facts are best explained by the assumption that the common basic origin of all these pathologic conditions, that is, the constitutional biologic inferiority of the auditory organ, is produced by an alteration of two mendelian genes that under normal circumstances secure normal development, structure, and function of the auditory organ It is not necessary to discuss in more detail the methods applied and the facts obtained in our studies that induced the aforementioned conclusions What matters here is that a constitutional biologic inferiority of the auditory apparatus occurs in certain strains

8 Thyroid

Both hyper and hypothyroidism as well as simple goiter are known to occur in several members of a family throughout generations[5] What matters here with regard to constitutional biologic inferiority of the thyroid is the fact that one or several

members of a family may suffer from hyperthyroidism, others from a simple goiter[25] or perhaps myxedema. In a case I observed, it is hardly coincidental that the grandmother died of a cancer of the thyroid gland and the granddaughter has an infantile myxedema. Recently the cases of two brothers with sporadic cretinism have been reported in this country.[49] Their sister and two of the mother's first cousins had thyroidectomies; the mother's sister is reported to have an enlarged thyroid gland. We must assume an inheritable constitutional weakness, a constitutional biologic inferiority of the thyroid, predisposing it to different kinds of pathologic alterations.

9. Digestive Tract

An instructive instance of constitutional biologic inferiority has been furnished by extensive studies carried out with my former associate, Dr. Berta Aschner, on the families of 255 individuals with peptic ulcer.[26] First of all, the existence of a hereditary factor in the etiology of peptic ulcer of the stomach and duodenum was confirmed on a large scale. If both parents of an ulcer patient were free of any stomach trouble, 10.8 per cent of their children developed ulcer. If one of the parents had some kind of chronic stomach trouble, 25.7 per cent of their children suffered from ulcer.

The question that arises is: What genetic factor is instrumental in the development of a peptic ulcer? The answer is to be gathered from table 1. As the first vertical column demonstrates, peptic ulcer is found almost five times as frequently in the families of patients with peptic ulcer as in the control families. The second column demonstrates that cancer of the stomach is found almost four times as frequently in the families of ulcer patients as in the families of the controls. This fact, published about twenty years ago, has since been confirmed by other authors. The third and fourth columns of the table demonstrate that cancers of the digestive

tract other than gastric cancer, and other chronic diseases of the stomach, are to be encountered far more frequently in the ulcer families than in the controls

What is it then that is transmitted through the germ plasm and accounts for the evident predisposition to peptic ulcer, cancer, and various other disorders of the stomach? It can be nothing but a constitutional biologic inferiority of the stomach bearing upon its structure, quality, and reactivity As a matter of fact, the cancer in these families can by no means be considered as always due to malignant degeneration

TABLE 1

	In the family are to be encountered			
	Peptic ulcer	Carcinoma of the stomach	Carcinoma of the digestive tract	Any chronic stomach disease (ulcer carcinoma, gastritis, nervous dyspepsia)
	Percentages			
255 cases of peptic ulcer	17 25 ± 6 69	13 73 ± 6 1	17 25 ± 6 69	53 33 ± 8 84
400 cases of various diseases other than affections of the digestive tract	3 5 ± 2 6	3 5 ± 2 6	4 75 ± 3 01	15 25 ± 5 08

of a peptic ulcer From the genetic point of view, duodenum and stomach form a biologic unit that is itself a part of the greater unit represented by the whole gastro-intestinal tract

There may even be some evidence of a morphologic or functional basis for the biologic inferiority of the stomach and duodenum, detectable only in a manifest familial constitutional predisposition to disease, or in a lowered resistance to extrinsic or intrinsic injuries of any sort, including excessive nervous and psychic impulses Not infrequently small islands of displaced embryonic tissue may be found in the gastric mucosa, some representing dystopic intestinal mucosa and some

members of a family may suffer from hyperthyroidism, others from a simple goiter[25] or perhaps myxedema In a case I observed, it is hardly coincidental that the grandmother died of a cancer of the thyroid gland and the granddaughter has an infantile myxedema Recently the cases of two brothers with sporadic cretinism have been reported in this country[49] Their sister and two of the mother's first cousins had thyroidectomies, the mother's sister is reported to have an enlarged thyroid gland We must assume an inheritable constitutional weakness, a constitutional biologic inferiority of the thyroid, predisposing it to different kinds of pathologic alterations

9 *Digestive Tract*

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The question that arises is *What genetic factor is instrumental in the development of a peptic ulcer?* The answer is *to be gathered from table 1* As the first vertical column demonstrates, peptic ulcer is found almost five times as frequently in the families of patients with peptic ulcer as in the control families The second column demonstrates *that* cancer of the stomach is found almost four times as frequently in the families of ulcer patients as in the families of the controls This fact, published about twenty years ago, has since been confirmed by other authors The third and fourth columns of the table demonstrate that cancers of the digestive

ance and function of the gastric mucosa and the patient's mood and emotional reactions. Various emotional states such as fear, sadness, anxiety, hostility, or resentment were found to be accompanied by either pallor of the gastric mucosa, inhibition of acid secretion, and contractions, or by hyperemia and engorgement of the mucosa, hypersecretion, and hypermotility. In the latter state the gastric "folds became thicker and succulent and the lining of the stomach presented the picture designated by gastroscopists as hypertrophic gastritis." During such a temporary state, mucosal erosions and hemorrhages were readily induced by even the most trifling traumas, and frequently bleeding points appeared spontaneously as a result of vigorous contractions of the stomach wall. Protected by an efficient insulating layer of mucus, these small erosions healed promptly within a few hours. If, however, the protective mucus was sucked away and the erosion was exposed to acid gastric juice for several days, the lesion increased in size and presented the punched-out appearance of a chronic peptic ulcer with well defined edges and a granulating base.

Again we must face the fact that biologic inferiority of an organ may act as the determining factor with regard to the symptomatology of nervous and psychoneurotic disorders, endocrine diseases, or allergic conditions. Whether gastric symptoms do or do not come to the fore under these circumstances, may depend largely on the constitutional biologic worth of the stomach. We shall discuss later how other genetic factors and environmental influences must concur with the constitutional biologic inferiority of the stomach in order to produce an actual disease. They also decide whether such a person becomes afflicted with peptic ulcer, gastric cancer, gastritis, or nervous indigestion. The important ro[illegible] of biolo[illegible]

far as

dystopic pancreatic tissue Many authors consider this dystopic tissue the point of origin of ulcerations or malignant growths Even in peptic ulcers of the jejunum such displaced embryonic cells have been found as an apparently predisposing causal factor

It is easily understood that gastritis of any variety is likely to develop in a stomach with lowered viability of its structural elements Whether and to what extent chronic gastritis is a predisposing factor in the development of both peptic ulcer and cancer has not yet been settled It seems to me, however, that the diagnosis of gastritis chiefly on the basis of gastroscopic examination is made too frequently today Subjective symptoms of gastric distress and objective gastroscopic signs do not always correlate with one another Hyperemia and emigration of leucocytes on the mucous surface are physiologic events connected with the digestive function The height and width of the gastric rugae depend on the tonus of the nonstriated gastric muscles, which in turn is regulated by the nervous system The gastroscopic picture has been found to vary with the functional state of the stomach It seems to me that if from 40 to 50 per cent of all patients examined with the gastroscope are reported to have gastritis, and if thorough clinical study of these patients reveals so-called personality disorders with a surprisingly high frequency, the term gastritis is not always justified Hyperirritability and hypersensitivity of the stomach due to its biologic inferiority may result in "nervous dyspepsia" or "nervous indigestion" These may frequently be more correct terms than gastritis, since the presence of an actual inflammatory process in such a stomach is rather doubtful

An important contribution to this problem, corroborating our view, was made by Wolf and Wolff[47] A patient with a large gastric fistula, whose mucosa was readily accessible to view, was studied with regard to relations between the appear-

spaces around the liver cells instead of being secreted into the biliary capillaries, such a supposed state is known as paracholia. Physiologic constitutional hyperbilirubinemia, according to its degree, may or may not result in jaundice that, as a matter of fact, is a constitutional nonhemolytic jaundice. Careful studies of Dameshek and K. Singer[33] suggest that this type of jaundice may be due to a heightened threshold of the hepatic cells as regards the excretion of bilirubin. Such a "constitutional hepatic dysfunction" would result in a retention of bilirubin in the blood, since it is not excreted properly by the liver cells. The van den Bergh reaction is of course of the indirect type. A similar condition was described in a strain of rats with hereditary jaundice, and the same interpretation of this condition was given by Malloy and Lowenstein.[34, 59] Histologic examination of the liver in the jaundiced rats failed to reveal any abnormality. An equally negative result was obtained by liver biopsy in several cases of constitutional nonhemolytic jaundice in man.[48] This bespeaks a functional abnormality of the liver cells due to a pathologic gene.

In this connection it is worth mentioning a most peculiar condition that was observed by Steensma[35] in seventeen members of a family through four generations. The affected persons presented *orthostatic urobilinuria*, that is, the urine contained abnormal amounts of urobilin if excreted in the upright position but was free of urobilin if excreted when the patient was lying down. Steensma postulated an incompletely obliterated ductus venosus Arantii, so that blood passing from the intestine and containing urobilin could conceivably escape from the liver into the general circulation through the old fetal route. Mechanical conditions due to upright or recumbent position might have an influence upon the passage of blood through the ductus venosus. Whatever the correct interpretation of the pathogenetic mechanism may be, the

discussion It stands to reason that constitutional biologic inferiority may result in abiotrophy and premature senescence of certain organs

Regional enteritis is not a frequent disease The fact that it has been observed in a brother and sister,[27] and, in another instance, in two sisters and one brother,[28] is at least suggestive of a constitutional (Crohn[27] spoke of a congenital) predisposition to this inflammatory disease If so, only a biologic inferiority of the intestines would account for such a predisposition

The existence in certain individuals of a "hepatic weakness," constitutional in nature, has recently been postulated by Boyce[29] He arrived at the concept of the "liver weakling," that is, an individual born with a congenital hepatic inferiority, by studying "liver deaths" and the "hepatorenal syndrome" occurring unexpectedly after any sort of surgery and any type of anesthesia Boyce based his assumption of a "constitutional hepatic inferiority" on the fact that Quick's hippuric acid test of liver function occasionally revealed unexpectedly low values in presumably normal and healthy persons who were studied as controls Postoperative depression of liver function, which follows all surgery, may in Boyce's opinion become serious and even fatal in such constitutionally inferior subjects They are poor surgical risks and need particular protection

Boyce is not aware of the fact that his concept of constitutional hepatic inferiority has predecessors There are persons with extraordinarily high amounts of bilirubin in the blood serum, without manifest disease This state occurring as a familial trait was first described as *cholémie familiale simple* by Gilbert and Lereboullet[30] Van den Bergh and Snapper[31] called it "physiologic constitutional hyperbilirubinemia" In collaboration with E A Spiegel, I assumed[1,32] that in such individuals part of the bilirubin is secreted into the lymph

(congenital abnormal fragility of the bones) Osteoblasts, chondroblasts, fibroblasts, and odontoblasts have been involved in such cases In so-called lymphatism, a systemic biologic inferiority of all mesenchymal derivatives has been postulated by Pfaundler,[11] the eminent pediatrician It is held to pertain to the connective tissue, the blood vessels, the lymphatic apparatus, and the nonstriated muscle system, all of these being abnormally irritable but at the same time liable to precocious wearing out

12 Ectoderm

The typical combination of hereditary abnormalities of the teeth and of the appendages of the skin points to a genetically founded biologic inferiority of large parts of the ectodermal germinal layer Aplasia or hypoplasia may in such cases involve the teeth, the sweat glands (anhidrosis), the sebaceous glands, and the hair Mental defects may indicate a farther reaching ectodermal anomaly Extreme cases of hypertrichosis—so-called human canines or 'dog faced men," as they are occasionally seen in show booths—show as a rule developmental anomalies of the teeth [8]

13 Racial Differences

A trait that was originally constitutional, and has become familial by hereditary transmission, may eventually become

population that

istic Clinical experience ga

with regard to their mesenchymal derivatives The greater frequency of extreme hyperextensibility of metacarpophalangeal and interphalangeal joints, of high grade cubitus valgus, of pinguecula, of prominent and tortuous temporal arteries in young individuals, and the well

etiologic factor in this orthostatic urobilinuria is a pathologic gene—according to Steensma's belief—preventing the normal obliteration of a fetal venous pathway.

10. Connective Tissue

Eminent physicians around the beginning of the twentieth century tried to achieve a unitary and more satisfactory comprehension of various abnormal physical conditions by assuming a biologic inferiority of certain tissues rather than of organs. Static disorders of the skeleton, hernias, varicosities, visceroptosis, prolapsus, etc., were attributed to constitutional weakness of the connective tissue throughout the body. Biologic inferiority may comprise the tendency to excessive proliferation of the connective tissue, in order to make up by quantity for the inferior quality. Such a "fibroplastic predisposition" of some persons was supposed to account for the formation of keloids, extensive postoperative peritoneal adhesions, postinflammatory pleural and pericardial adhesions, joint ankyloses and contractures. Payr[36] recommended that patients should be checked for their fibroplastic predisposition before surgical procedures. It was considered that the method of surgical treatment and the postoperative management should allow for such an individual peculiarity. Scars resulting from former vaccination or from purposely inflicted test incisions, it was held, would give the required information about a person's fibroplastic tendency. An anatomic basis for the individual differences in functional behavior of the connective tissue has been found by a pathologist, Hueck.[37] The fibrous elastic network of arterial walls can vary widely with regard to both the density of the meshes and its content of elastic fibers. A selective weakness of the elastic tissue has been supposed in certain conditions.

11. Mesenchyma

A widespread constitutional inferiority of mesenchymal derivatives has been assumed in cases of osteogenesis imperfecta

important facts discussed in this chapter. No attempt has been made to review all the evidence available concerning the existence of constitutional biologic inferiority of organs and tissues. Yet the instances discussed here should suffice to illustrate and prove the importance of such loci minoris resistentiae in the etiology of diseases.

known tendency to keloids in Negroes, are indicative in this respect. The high frequency of essential hypertension, particularly of its malignant variety, of endo- and myocardial lesions, of uterine fibroids, and of prostatic hypertrophy, and, last but not least, the occurrence of the sickle cell trait with subsequent sickle cell disease in the Negro race, militate in favor of a racial difference as far as the reactivity, the biologic worth, and the morbidity of mesenchymal and mesodermal derivatives are concerned.

14. Unilateral Inferiority

Most puzzling are rare occurrences demonstrating that a constitutional biologic inferiority may pertain to one side of the human body. A few instances will illustrate this situation. *A young man has an asymmetric face by reason of hypoplasia* of its left side. The pigmentation of the fundus oculi is less marked and the retinal arteries are narrower in the left than in the right eye. The left testicle is hypoplastic.[39] In another family a man with a large vascular nevus on the right arm and right half of the chest develops a postdiphtheric palsy of the right arm. His mother has the same kind of nevus on the same portion of the body, also an aplasia of the right pinna, a peripheral paralysis of the right facial nerve, and amblyopia of the right eye. His brother has a clubfoot on the right side, the grandmother a facial asymmetry due to a lagging innervation of the right facial nerve.[40] Another author reports a case of heterochromia of the iris with iridocyclitis and a cataract of the lighter eye, and with hardness of hearing due to a labyrinthine lesion on the same side.[41] In this connection the cases of partial gigantism affecting either an entire half of the body or face, or single extremities or their parts, are pertinent.

Such rare events as a matter of fact are only of academic interest. Nevertheless, they deepen the knowledge and comprehension of less obvious but far more frequent and clinically

are regulated to a variable extent by the endocrine organs and the nervous system The principle of mutual check and balance characterizes constitution in both the sociologic and the biologic sense of the word

The condition of the skin, growth of hair, amount and distribution of adipose tissue, metabolic functions—including the basal metabolic rate—pulse rate and blood pressure, blood count, gastric acidity, gastro-intestinal motility, urine production, perspiration, sexual functions, wound healing, production of antibodies, and many other functions of the organism are regulated by both the endocrine and the nervous system They are, however, dependent in the first instance on the proper condition of the structures and organs involved primarily in the production and maintenance of the respective traits and functions

Constitutional tendency to excessive perspiration, for instance, may be due either to a hyperirritability of the autonomic nervous system, to an excessive supply of thyroid hormone, or to an excessive intrinsic function of the sweat glands and an abnormal readiness on their part to respond to nervous and hormonal stimuli Sexual impotence in a man may be produced either by a lesion of particular spinal centers, by a deficiency of the testicular hormone, or by a primary cerebral or psychic disturbance

The term *principle of treble safeguard* has been used to postulate the fact that many traits and functions of the organism are dependent on and regulated by the proper cooperation of (*a*) the relevant organ ("effector organ," *Erfolgsorgan*), (*b*) the endocrine system, and (*c*) the nervous system In the instances cited above, the sweat glands and the spinal sex center, respectively, would represent the effector organs The scheme of figure 2 will clarify this situation The relationship of the three factors in securing the proper development of a trait or the proper function of an organ may show individual variations Abnormality of a trait or func-

IV

THE INTEGRATIVE SYSTEMS OF INDIVIDUAL CONSTITUTION—I

TO SOME extent constitution in the biologic sense of the word is comparable to the notion of constitution in sociology In the latter science, constitution is defined as "the fundamental law according to which the government of a state is organized and the relations of individuals with society as a whole are regulated "[1] This *regulation is* accomplished by legislature, administration, and judiciary, all of them cooperating with and dependent on one another In *many respects, however, the individual person is not dependent* on these regulating powers and can—at least in democratic states—do what he pleases

In a previous chapter the biologic constitution of an individual was defined as the panel and plan of his personality, potentially determined at the moment of fertilization, and represented by the genes localized in the chromosomes of the fertilized ovum This is the fundamental law governing the differentiation of the rapidly multiplying cells and the formation of the various tissues and organs, their future function and biologic worth, and their proper interrelation and cooperation Each cell or organ depends on its fellow cells and organs so far as its functional efficiency is concerned, each of them requires a normal function of the circulatory, hemopoietic, digestive, and *other organ systems A preferential integrative function,* however, is exercised by the highly specialized endocrine system on the one hand and the nervous system on the other Practically *all activities of the organism, both physical and mental,*

the tissues, and thus it is indirectly involved in the pathogenetic mechanism of diabetes insipidus Large doses of estrogenic hormone may also in certain cases check the clinical picture of diabetes insipidus, but it does not follow from this that ovarian insufficiency is a causative factor Such an assumption would be as little justified as the preposterous belief that the lack of mercurial diuretics has something to do with diabetes insipidus, on the premise that the administration of such diuretics has been shown to relieve its signs and symptoms temporarily[1]

1 The Endocrine System, Endocrine vs Constitutional Anomalies

a) THE ENDOCRINE SYSTEM AS MEDIATOR BETWEEN CONSTITUTION AND EFFECTOR ORGANS

Growth—Height of the body is genetically determined and modified to a certain extent by environmental factors Nourishment, especially vitamins, as well as sunlight, physical exercise, etc, are known to modify the growth of the body Yet these are of secondary importance as compared with the constitutional tendency to reach a certain height in a definite time Height is one of the foremost among characteristics differentiating human races What has become a racial trait must first have been a familial and therefore a constitutional one The growth and definite height of vertebrates is largely dependent on the proper function of some of the endocrine glands Disorders of the anterior lobe of the pituitary, the thyroid, the suprarenals, or the gonads may be associated with marked disturbances of growth gigantism and dwarfism may be induced by diseases of these endocrine organs It is unnecessary to describe in more detail the effects on growth of tumors, destruction by various pathologic processes, or malformations of these glands Such facts are to be obtained from textbooks of endocrinology, physiology, and medicine What we want to emphasize here is the necessity of taking into account not

tion may be produced by abnormality of one or more of the three factors. Individual differences of symptomatology in various diseases are frequently accounted for by such differences in the cooperating regulating factors. Cognizance of this fundamental principle of organization of the vertebrates is not only helpful but sometimes indispensable in order to avoid erroneous conceptions with regard to various pathologic conditions chiefly of constitutional origin. We shall frequently refer to the principle of treble safeguard in the latter portions of this book.

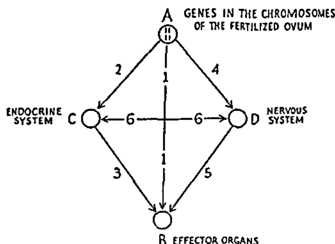


Figure 2

The intricate organization of the human individual requires a broader view on the part of its students than the customary narrow outlook. Many traits and functions ought to be envisaged as complex biologic units and cannot be understood by solely considering single parts of the integrative system. One instance may serve as an illustration. If total thyroidectomy relieves diabetes insipidus in some cases,[2] this does not mean that the thyroid plays an essential primary role in the pathogenesis of diabetes insipidus. The thyroid is known to promote the mobilization of water and sodium chloride from

glands in different stages of embryonic life accounts for these racial differences, normal glandular balance being resumed shortly thereafter Such an assumption is not supported by facts, and it is more than debatable whether the embryonic thyroid or pituitary is of any functional value at those earliest embryonic stages at which the achondroplastic extremity is known to be present

Stockard's extensive and painstaking studies on various races of dogs have been published in a large monograph[46] It is gratifying that Stockard no longer maintains his own theory A causal connection between a characteristic thyroid or pituitary pattern and a given bodily type could not be substantiated

The racial differences under discussion are brought about by genic differences acting directly on the effector organs of growth, that is, on the epiphyseal cartilages In our scheme, pathway 1, *leading* from A to B, must be considered first, C, that is, the growth regulating endocrine system, is not primarily involved in the racial differences of A mentioned thus far

Even human races have been related to special endocrine constitutions The Caucasian races were supposed to have a relative preponderance of the anterior pituitary as compared with the Mongolian or the Negro race Differences in the thyroid function, according to this theory, account for the Mongolian type, in the suprarenal function for the Negro type (Keith)[4] As a matter of fact, the endocrine constitutions of various races do show remarkable differences The thyroid both in the Malayans in the Dutch East Indies and in the Japanese has been found to be smaller than in the white races The thymus in the Chinese is larger and undergoes involution later than in Europeans The racial differences, however, are not induced by parallel differences in the endocrine constitution What has been said about this problem in relation to dogs holds true for human races too The Japanese may or may not be hypothyroid, but he is not

only pathway 3, or at best pathways 2 and 3 in our scheme (fig 2), but also pathway 1 In other words, we must embrace the whole biologic unit of growth, comprising all tracks leading from the genes (A) to the effector organs of growth (B), that is, the epiphyseal cartilages

Such outstanding authorities as Sir Arthur Keith and C R Stockard[4] referred to the endocrine system to explain not only racial differences of growth and height but also freak types of development and shape in various races of dogs The bulldog, St Bernard, dachshund, Boston terrier, griffon, and others were considered as special races, the form and appear ance of which are attributable to definite abnormalities of the glands of internal secretion These hereditarily defective glands were held to produce the particular racial pattern Yet the superficial resemblance to certain endocrine anomalies found among various kinds of mammals is the only but by no means sufficient argument in favor of this theory Neither anatomic nor functional abnormalities of the endocrine glands characteristic of the various races can substantiate the theory It is possible today to produce artificial acromegaly and gigantism in dogs by prolonged administration of pituitary growth promoting hormone, and it is possible to produce dwarfism by removal of the pituitary or thyroid It is impossi ble, however, to transform one canine race into another by means of endocrine control An artificially produced acromegalic giant dog is neither a St Bernard nor a Great Dane

Stockard advanced a hypothesis that would explain localized achondroplastic conditions as resulting from hereditary modifi cations of the endocrine glands Why do the dachshund and basset hound have short bent legs, while their heads and bodies are normally developed? And why do the Boston terrier and French bulldog exhibit achondroplasia limited to the head and vertebral column, the extremities being normal? Accord ing to Stockard a brief temporary disturbance of the endocrine

ment, and of the span over the height, is to be met with not infrequently in persons whose gonads failed to develop Hence the term *eunuchoid proportions* of the body Yet the situation is by no means as simple as that It is not justifiable[11] to relate the stocky, short legged type to early gonadal development and the thin, long legged type to retarded gonadal development[7]

Eunuchoid proportions sometimes are found in dwarfs, particularly in pituitary dwarfs, and may also be present in normal children Delayed epiphyseal union and consequent prolonged growth of the long bones cannot, therefore, account for the disproportionate length of the extremities in such persons Some Negro races show marked eunuchoid proportions and yet are by no means hypogonadal Nor is puberty in these races retarded These facts are at variance with the usual endocrinologic interpretation They prove that genetic factors bearing directly upon the epiphyseal cartilages and the growth rate must be paramount Hence it is evident that track 1 of our scheme, leading from A to B, that is, from the genes to the effector organs, must not be forgotten by those endocrinologists whose interest is usually limited to track 3, or at best to tracks 2 and 3

On the other hand, it must be kept in mind that the constitutional anlage for a definite height (localized somewhere in the chromosomes of A) is the ruling factor, and involves the endocrine system (C) in so far as the latter stimulates or checks the growth Pathways 1, 2, and 3 may be used for the phenotypical presentation of this particular anlage They all represent one biologic unit fulfilling the potentiality displayed by special genes of the germ The entire endocrine system, therefore, may be altered in various ways if one of its ruling genes—in our example, the gene determining height—deviates from the normal

Several cases of eunuchoid gigantism are on record[8] in which the families included several other giants, though not

hypothyroid because he is Japanese, and no hypothyroid person belonging to another race has ever become a Japanese for this or any other reason The racial differences in the endocrine balance may, however, account for some particular features of personality in various races and for racial differences in morbidity Graves' disease, for instance, is known to be extremely rare in the Dutch East Indies Yet the racial differences themselves are produced chiefly by track 1 of our scheme, leading directly from the genic structure of the fertilized ovum (A) to the effector organs (B) This is seen in lower metazoa and in plants, which are not provided with special endocrine organs G R Hoskins,[8] among the American endocrinologists, rightfully shows a reluctant and skeptical *attitude toward the theory advanced by Keith, in stating* "Considerable ingenuity is required to make it fit the facts

Since it has been known that the ossification of the epiphyseal cartilages depends on the maturation of the gonads, it has become customary to relate certain proportions of the body to special endocrine patterns Tandler and Grosz[9] were the first to demonstrate that persons with primary hypogonadism (castrates, eunuchoids) possess potentiality for growing in height over a longer period of time than normal individuals, because of the delayed ossification of the epiphyseal cartilages of the long bones The activity of growth promoting glands, such as the pituitary and the thyroid, are held to decide whether or not excessive growth of the extremities actually takes place The comparative length of the extremities has therefore been used for the diagnosis of certain endocrine types In the normal adult, the upper measurement (the distance from the symphysis pubis to the top of the head) is equal to the lower measurement (*the distance from the symphysis* pubis to the sole of the foot when the person stands), and the total height is equal to the span (the distance between the horizontally outstretched arms) As a matter of fact, a marked preponderance of the lower over the upper measure

significance," is the conclusion of Varney, Kenyon, and Koch[74] This is a full confirmation of the view expressed by the author in 1927[85] Hence the clinical syndrome has not been unknown and its interpretation was given long ago Albright[15] mentions that some of his subjects had relatives of short stature, and emphasized the frequency with which other congenital anomalies are met with in this condition—such as congenital webbing of the neck (pterygium colli), cubitus valgus, coarctation of the aorta, cleft palate, squinting, epilepsy, epiphysitis" (which is, according to Albright's figure 5, Scheuermann s disease of the vertebral column), and others The ovarian hypoplasia itself is in my opinion only a part of the widespread constitutional anomaly, of a multiple genetic defect that will be discussed later as "status degenerativus" A recent publication by Wilkins and Fleischmann[105] on 'ovarian agenesis" is in full accord with this concept

What has been said about constitutional overgrowth as resulting from an abnormal gene holds *true* for the opposite constitutional anomaly, that is, for undergrowth and dwarfism That the complex biologic unit comprising both the peripheral effector organs and the regulating endocrine system is ruled by a gene or a combination of genes, is clearly demonstrated by occasional instances spontaneously supplied by nature

There are so-called *primordial dwarfs*, that is, some kind of miniature editions of human beings, without any signs of abnormality of endocrine or other organs The pygmies of central Africa prove that such a constitutional deviation may become a racial characteristic

There are also *pituitary dwarfs* (midgets), whose pituitary deficiency results from abnormal genes affecting the structure and function of the anterior lobe of the pituitary This is proved by numerous reports on several members of a family, chiefly siblings, exhibiting pituitary dwarfism[10] I have seen identical (uniovular) twins who were both pituitary

of the eunuchoid type The following examples reported by the author may illustrate this situation

The first case was that of a 30-year-old giant (202 cm in height) with the typical enuchoid physique His extremities were of excessive length, his genitalia infantile He had never experienced any sexual desire, had no beard, and only very scanty hair of the axillae and pubis The patient's father was about the same size as his son, but obviously not eunuchoid The patient's brother measured 196 cm and two of his sisters were also unusually tall

Another eunuchoid giant, 32 years of age, who after several years developed a pituitary tumor, had a grandfather 205 cm in height, weighing 136 Kg

A similar family has been reported by Joedicke[9] and another recently by Mansbacher[72]

It is known that only a limited number of all eunuchoids are oversized It seems justified therefore to say that the eunuchoid giant is not a giant merely because of his being eunuchoid, rather, he is eunuchoid because he has the familial trend to gigantism It is evident that a thorough understanding of such abnormalities cannot be obtained merely by studying the glands of the affected person, but that it requires a far reaching study of his constitution and consequently of his entire stock This view has been expressed many times for more than twenty years[8] and has recently been corroborated by an editorial in the *Journal of the American Medical Association*[76] If it is not heeded, and if the genetic aspect of the problem is neglected, questionable and untenable conclusions must be the result[73, 77]

It has also been known for a long time that some female eunuchoids, that is, individuals whose ovaries are primarily hypoplastic or aplastic, may not be tall but on the contrary short in stature[8b] This deficiency in growth is not due to hypopituitarism, as was proved by both autopsy reports and assays of the gonadotropic hormone in the urine[74, 75] Attempts to explain this syndrome on a purely endocrinologic basis[75] are unsatisfactory "The association of growth and ovarian defects may be of genetic rather than of physiologic

significance," is the conclusion of Varney, Kenyon, and Koch[74] This is a full confirmation of the view expressed by the author in 1927[85] Hence the clinical syndrome has not been unknown and its interpretation was given long ago Albright[75] mentions that some of his subjects had relatives of short stature, and emphasized the frequency with which other congenital anomalies are met with in this condition—such as congenital webbing of the neck (pterygium colli), cubitus valgus, coarctation of the aorta, cleft palate, squinting, epilepsy, "epiphysitis" (which is, according to Albright's figure 5, Scheuermann's disease of the vertebral column), and others The ovarian hypoplasia itself is in my opinion only a part of the widespread constitutional anomaly, of a multiple genetic defect that will be discussed later as "*status degenerativus*" A recent publication by Wilkins and Fleischmann[105] on "ovarian agenesis" is in full accord with this concept.

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dwarfs[11] Extensive studies have been devoted to the peculiar strain of dwarf mice reared and first described by P E Smith and McDowell[12] These mice were pituitary dwarfs, they lacked eosinophile cells in the hypophysis and failed to produce the growth-promoting hormone in this gland Administration of the hormone induced rapid growth in such dwarf mice The defective pituitary gland was shown by breeding experiments to be due to a recessive mendelian unit

Achondroplasia or *chondrodystrophic dwarfism* is characterized chiefly by excessive shortness of the extremities It is due to a constitutional anomaly of the epiphyseal cartilages that prevents normal cell proliferation, which leads to lengthening of the long bones The cartilage cells have been found to be hypoplastic in various degrees, or sometimes even more severely altered, in that they show irregular arrangement or mucoid degeneration This latter condition is called malacic achondroplasia, and is observed only in the newborn, since such individuals usually are not viable Achondroplasia is an inherited type of dwarfism, the abnormal gene acting chiefly upon the epiphyseal cartilages The qualification "chiefly" indicates a possible repercussion of the abnormal gene on structures and organs other than the epiphyseal cartilages Achondroplastic dwarfs often show marked signs of hypergenitalism Their external genital organs are often unusually large, the secondary sex characteristics are very well developed, the puberal changes take place at an early age, and sexual activity is sometimes particularly high Achondroplastic dwarfs usually are highly intelligent and because of their witty, hypomanic temperament were employed as court jesters and are at a premium as clowns Constitutional hypergenitalism, however, is by no means the cause of achondroplasia but at best the result of a far reaching effect of the abnormal gene acting upon the enchondral ossification directly Such a mechanism is also suggested by the frequent occurrence of cartilaginous exostoses in the neighborhood of the epiphyseal junctions

The varieties of constitutional dwarfism thus far discussed are produced by different genes, the first acting upon the size of the body quite generally, the second acting upon the anterior pituitary lobe, the third acting upon the rate of enchondral growth of the long bones They are, however, connected with one another and form a biologic unit, ruling the height of the body This is indicated by the occurrence of various types of dwarfism in the same family In 1924 report was made of a family[11] in which the mother was a primordial, that is, a *proportionate* dwarf, without any symptoms or signs of endocrine disturbance, one daughter was a rachitic dwarf, and a second daughter represented pituitary dwarfism The latter was 39 years old, had marked hypoplasia of the genital organs, eunuchoid physique, and undeveloped secondary sex characteristics, and had never menstruated Similar observations have been made by other authors [8b, 10]

Most interesting is a freak of nature, reported many times in the literature, that is more than suggestive in relation to considering growth as a complex biologic unit *represented* in the germ plasm It cannot be pure coincidence that various kinds of growth disorders such as gigantism, partial gigantism, acromegaly, and dwarfism are found in members of the same family [4a, 4b, 8d, 16] Here are a few illustrations of this situation

P Stewart[13] reported the case of a 20-year-old man with general myoclonus who had stopped growing at 14 but who had developed normal genitalia His sister had stopped growing at 12 but had menstruated since her fourteenth year Five siblings of the same parents were born prematurely because of their excessive size, seven others were also abnormally large at birth and not viable A twin child observed by Allaria[14] had partial gigantism of three fingers of his right hand, his mother was acromegalic and had a goiter Koehler[16] describes two sisters, of whom one had partial gigantism of the first two toes of the right foot, while the other sister was a dwarf I published the picture of two sisters,[4d] one affected

with achondroplasia and measuring only 121 cm in height, the other presenting constitutional proportionate oversize (height 183 cm) without any abnormalities of the endocrine system or other organs A brother of the two sisters measured 190 cm, another sister measured 185 cm and weighed 125 Kg, both parents also were very tall

We are far from a satisfactory understanding of the genetic basis of such occurrences We know, however, that constitutional pathology and not merely endocrinology must lead us in our endeavor to comprehend these incidents The glands that regulate growth may or may not be involved somehow by an abnormality of the gene complex ruling the growth function The repercussion of such abnormal genes on these glands may create a "weak spot" in that particular part of the body The endocrine glands therefore may become victims of a biologic inferiority predisposing them to the formation of cysts, tumors, or tuberculous or other lesions Where such conditions of the endocrine glands are encountered in association with disorders of growth, the causal connection is not necessarily as simple as it would seem from a purely endocrinologic standpoint The actual disease of an endocrine gland may occasionally be the indirect and remote consequence rather than the cause of the abnormal growth Such a concept may sound more philosophic than scientifically founded, however, in my opinion it represents the only way of approaching the facts with true scientific curiosity

The term *endocrine stigmatization* is used[16] for those structural and functional deviations of the endocrine system that ought to be considered as indicators and side effects of an abnormal constitution rather than as the underlying cause of a particular constitutional disorder We shall frequently encounter the principle of endocrine stigmatization in further portions of this book

Evolution and Aging—The same general laws that rule growth govern evolution and aging The speed of both maturing and withering is determined by the germ plasm Regard

of genes representing the individual constitution Much has been written in the past on longevity as an inheritable characteristic Most of the credit for this work should be given to Raymond Pearl[17] The racial differences with regard to the onset of both puberty and menopause are of common knowledge Unusually early or delayed puberty or menopause, as compared with the normal average of the race, is occasionally encountered as a familial trait The intercalation of the endocrine system between the respective genes and the effector organs is even more obvious with regard to evolution and aging than with regard to growth In other words, in our scheme, pathways 2 and 3 are paramount as compared with pathway 1

Evolution It is important to adhere to a clear-cut terminology in this field The term *infantilism* designates an *arrest* of development, the abnormal persistence of an evolutionary stage beyond the normally appropriate age The word was introduced into the medical literature by Lorain in 1871 [illegible] Tandler[illegible] distinguished universal from partial infantilism on the basis of whether the whole organism or only some of its organs showed delayed development Such partial arrest of development may be called fetalism, embryonism, puerilism, or juvenilism, according to the evolutionary stage that is persisting abnormally A left sided cecum, a fanlike appendix, a pelvic kidney, cryptorchidism, most of the congenital heart diseases, etc, would represent such partial arrests of evolution in fetal life Systemic hypoplasia of the cardiovascular system, infantile features in the psychic behavior of adults, persistence of high pitched voice in otherwise normal men, isolated failure to undergo the puberal evolution of the genital organs, that is, so-called eunuchoidism, are instances of partial infantilism There is little doubt that most of these instances of partial arrest of evolution are brought about by an abnormality of the very organ affected Since most of these abnormalities are constitutional in type, they are due to abnormal

genes (A) acting upon the effector organs (B) on track 1 of our scheme.

It may be mentioned that there have been reports of eunuchoidism occurring in several members of a family.[16,17] In this particular variety of partial infantilism an endocrine organ manifests itself as the effector organ. Yet eunuchoidism, that is, partial infantilism of the testicles or ovaries, differs entirely from universal infantilism, as much as does pituitary dwarfism. The latter engenders some signs of partial infantilism, such as arrest of growth and sexual development; a pituitary dwarf, however, is not an old child, especially not in so far as the mental condition is concerned.

Insufficient function of the thyroid, pituitary, or gonads starting in childhood is associated with developmental anomalies, with the persistence of certain infantile characteristics, but all of these cases are by reason of their special clinical pictures different from the rare cases of universal infantilism. Just as a child does not differ from an adult merely because of endocrine insufficiency of one or more glands, so universal infantilism is due not to a primary endocrine disturbance but to a general arrest of development affecting each cell of the body. The hypoplasia of the endocrine organs in these cases is not the cause of infantilism but a part of the general hypoplasia.

Universal infantilism is not necessarily constitutional in origin. Environmental factors, such as nutritional deficiencies, lack of sunlight, acquired diseases of long duration, impairment of vital functions owing to congenital syphilis, or congenital diseases of the heart may impede the realization of otherwise normal constitutional tendencies. What has been described in the past as cardiac, pulmonary, intestinal, hepatic, pancreatic, celiac, or renal infantilism belongs to this category and should be called *dystrophic infantilism* of Lorain's type.*

* In many textbooks and articles the term "Lorain-Levi type of infantilism" is used. This practice is not justified and should be abandoned. E. Levi in 1908 ascribed certain cases of infantilism to hypopituitarism. *Hypopituitary dwarfs*, however, are to be distinguished from persons with dystrophic infantilism.

The condition observed in young individuals affected with ulcerous colitis,[47] or that ensuing from gastrectomy performed in young monkeys,[48] is dystrophic infantilism Less frequent are those cases of universal infantilism in which retarded development cannot be accounted for by extrinsic factors If several members of the family are affected, a constitutional origin of the condition may be assumed as most probable Universal infantilism is not a frequent condition The goal of puberal development may be reached by such individuals, although late and often incompletely They may remain starvelings all their lives

It does not matter here what the actual mechanism of puberal evolution may be, or to what extent increased production of the gonadotropic pituitary hormone and the greater responsiveness to this hormone may be contributing The modern assays of hormones did and will supply us with invaluable information in this respect It must, however, not be overlooked that the underlying forces initiating the various changes in the endocrine system during puberty and climacteric lie in the chromosomes of the fertilized ovum Pathways 1, 2, and 3 of our scheme portray these forces

It is known that as a rule the first menstruation is preceded by the development of the breasts and by the growth of hair in the pubic region and in the axillae The signs of puberal maturation appear in a definite, timely order[49] Several years before the advent of these visible signs of maturation, the puberal adjustment of the endocrine system takes place At the age of 8 years, boys and girls begin to show a sexual difference in the excretion of the respective sex hormones, at 11, greater amounts of follicle stimulating pituitary hormone are to be recovered from the urine as compared with earlier ages[50] These facts demonstrate the biologic unity of the evolutional process, which consists of (a) the constitutional impulse (A), (b) the effector organs (B), whose responsiveness to hormonal impulses depends on A acting upon B on track 1 of our scheme, (c) the respective endocrine glands (C), acting upon the

effector organs (B) on track 3 and being themselves stimulated by the genic tendency (A) on track 2 (fig 2)

Knowledge of this intricate mechanism may be of practical importance Years ago I was consulted by a student, 23 years of age, whose only complaint was complete lack of a beard He was a handsome, strong boy of otherwise normal masculine physique, with well developed genital organs It was simply an inferiority complex that induced the young man to undergo all kinds of hormonal treatments Finally he ate fresh bulls' testicles over a long period of time, but without result What was actually wrong with this patient? It was not the constitutional drive to puberal maturation, nor was it the manner in which the endocrine system was responding to this drive It was obviously a constitutional abnormality of one particular effector organ, that is, of the skin, which was not responding to a normal hormonal stimulus in a normal way, that accounted for the patient's abnormality That this particular organ was a constitutionally "weak spot" in the patient's make-up could be concluded from the fact that he had been suffering from a severe generalized eczema several months before he came for advice

It is common knowledge today that hormonal therapy, particularly the administration of the anterior pituitary-like principle of pregnancy urine, may promote descent of the testes in some cases of *cryptorchidism* This fact, however, by no means proves that cryptorchidism is due to a primary endocrine defect Spontaneous descent of both unilateral and bilateral imperfectly migrated testes is so frequently observed that treatment does not seem to be warranted until puberty is well advanced[10] My own experience with glandular therapy is in accord with that of Thompson and Heckel,[11] who concluded that it is likely to be effective only in those cases in which the testes would descend normally without it at the time of puberty

By administration of the anterior pituitary-like principle

of pregnancy urine, Thompson and Heckel[21] were able to produce descent of the testes in 20 per cent of their cases, but failed in all cases in which the testicle was intra abdominal or deflected over the external abdominal muscle In the majority of cases of pituitary dwarfism, the testes, although hypoplastic and atrophied have descended The normal descent may be stimulated and hastened by the use of pituitary hormone, but it is due fundamentally to the genetically determined, constitutional capacity to attain the normal goal of somatic development at the proper time Persistent or temporary cryptorchidism is due to a genetic rather than to an endocrine abnormality, as is proved by its not infrequent occurrence in several members of a family[22] It is pathway 1 and hardly pathways 2 and 3 of our scheme upon which the causative factor originating from an abnormal gene operates Neither the pituitary nor the gonads show signs of an abnormal endocrine function in uncomplicated cases of cryptorchidism

Precocious puberty may occasionally be seen in several members of a family[26] In a family reported on by Rush et al,[27] the father showed signs of puberty at the age of 5 years, one son at the age of 3 years, the other son at the age of 18 months Five other instances of precocious development were found in four generations of the family The authors speak rightfully of a primary-constitutional pubertas praecox The term congenital, however, used by the authors synonymously, is incorrect, as the condition was not present at birth

Track 1 as well as tracks 2 and 3, the latter using the endocrine system as mediator, are available for the realization of the constitutional anlage It should be remembered that the nervous system (D) is also a part of the biologic unit under discussion It appears more and more probable that cases of precocious puberty associated with tumors of the pineal body are due to lesion of a hypothalamic nervous center rather than to pineal endocrine disturbance[28, 29] Whatever the mechanism made use of by the constitutional anlage in a

particular case, this anlage should be duly appreciated. Is it *not startling proof of its existence that identical twins brought* up in different environments show the same rate of growth, development, and maturation and may even start menstruating on the same day?

E. Novak[80] recently drew attention to the genetic variety of precocious puberty, which cannot be accounted for by any endocrine or central nervous disease. He reported 9 cases of this "constitutional type of female precocious puberty" and believes it to be the most frequent variety of sexual and somatic precocity. A male case belonging to the same category was published by McKenna et al.,[81] although it was differently *interpreted by the authors.*

Pubertas praecox is also one of the manifestations of a syndrome first described by F. Albright.[82-99] It is characterized by (*a*) multiple bone cysts that have a tendency to be unilateral in some cases, (*b*) brown-pigmented nonelevated areas of skin that tend to be on the same side as the bone lesions, and (*c*) sexual and somatic precocity, particularly when the disease occurs in females. This disease, known as *Albright's syndrome,* has been and is still being interpreted as resulting from a "disseminated neurologic lesion" involving especially the hypothalamic region. No sufficient proof has been offered for this hypothesis. There can be no doubt, in our opinion, that the polyostotic fibrous dysplasia that is the cause of the bone cysts, as well as the pigmented nevi, are of developmental, that is, of genetic rather than of hypothalamic *origin.*

Two cases of Albright's syndrome were thoroughly studied at autopsy. In one, the central nervous system, including the hypothalamus, was found to be normal.[100] In the other, reported by Albright et al., *an abnormality in the area of the* third ventricle was found; this was considered on histologic examination to be a congenital anomaly, exhibiting an accessory nucleus in the subthalamic area.[101] Hence the autopsy

findings do not support the assumption of hypothalamic origin, they do support, however, the theory of developmental causation of the syndrome

The intimate relation between Albright's syndrome and Recklinghausen's neurofibromatosis has recently been emphasized by Thannhauser[101] The pigmented areas common to the two diseases are birthmarks Their origin from structural changes of the finest skin nerves and the tactile corpuscles of Wagner Meissner is now generally accepted Their relation to the neurofibromas (neurinomas) of Recklinghausen's disease was first assumed in 1899 by Soldan[102] Thannhauser points out that the fibrocystic involvement of localized areas of the skeleton that is the main part of Albright's triad, but also occurs in Recklinghausen's neurofibromatosis, may have a pathogenesis similar to that of the pigmented areas of the skin Histologic features suggest that these fibrocystic lesions of the bones may originate from neurofibromas within the osseous tissue[106]

The genetic origin of Recklinghausen's neurofibromatosis is generally accepted It is only logical to assume that the third part of Albright's triad, that is, the sexual and somatic precocity, is of the same origin as its other parts, the fibrous dysplasia of the bones and the pigmented areas of the skin In other words, it is justifiable to assume that it is the constitutional variety of precocious puberty that is encountered in Albright's syndrome Linkage of recessive genes seems more probably the underlying causal mechanism than pleiotropism of a gene In the case of linkage it cannot even be expected that hereditary transmission of the full fledged syndrome of Albright will be observed in two or three generations of human beings

As usually occurs in various types of extensive genopathy, other genetic abnormalities may occasionally be encountered as a kind of constitutional trimming of the disease They are signs of a status degenerativus Such signs reported in

cases of Albright's syndrome include small testes in one, slight gynecomastia in another, diffuse goiter with an unusually large thymus and signs of hyperthyroidism in a third case, reported by Albright et al The elongation of the first and second metacarpals mentioned in one of these cases, and the marked hyperostosis, chiefly of the frontal bones of the skull, reported in the majority of the patients affected with the syndrome,[82 83 84] are probably indicative of a constitutional (genetic) abnormality of the skeleton As far as the frontal hyperostosis is concerned, its significance as a degenerative stigma will be discussed in a later chapter (p 181) The development of bone sarcoma in at least 3 known cases of polyostotic fibrous dysplasia has been mentioned above It can hardly be considered merely a chance coincidence In Coleman's case[103] of a 13-year old boy, autopsy revealed an extremely hypoplastic kidney, with hypertrophy of the other kidney, a partial coarctation of the aorta immediately beyond the arch, an aneurysm of the thoracic aorta, and an acute hemorrhagic pancreatitis In another autopsied case,[100] that of a 13 year-old girl, the findings comprised a Meckel diverticulum, patent foramen ovale, hyperplastic thyroid, thymus, and lymphoid structures, and basophilic hyperplasia of the pituitary Such alterations of endocrine glands reported in some cases of Albright's syndrome have the significance of endocrine stigmatization and do not justify endocrine theories[100 101] of the pathogenesis of the syndrome

Aging Attention has been given to the constitutional background of the aging process in an earlier part of this book At that point precipitated senescence in its relation to abiotrophy was discussed in so far as the aging process may involve various organs of the body at different times and to a different extent It is on track 1 of our scheme that the respective genes are operative in producing senile involution of selected organs Presbyopia, for instance, in part due to sclerosis of the crystalline lens and in part to a gradual weakening of the

ciliary muscle, illustrates a normal selective aging process widely independent of senile involution of the rest of the body The same holds true for graying of the hair, onset of the menopause, etc

Yet the endocrine system as mediator is intercalated between the constitutional tendencies (A) and the effector organs (B) in the process of involution as well as in that of evolution Diseases of the endocrine glands, such as the pituitary (Simmonds' pituitary cachexia), the suprarenals (Addison's disease), or the thyroid (myxedema), may be associated with more or less marked signs of precocious aging of the organism However, the plain theory still advocated by some endocrinologists, who ascribe senescence to a primary atrophy of the thyroid, gonads, or pituitary, is too simple and superficial to cover the facts This is particularly true as far as the gonads are concerned They themselves, like other organs and endocrine glands, are involved in the constitutional process of senescence but by no means initiate or produce it

Climacteric is but an easily perceptible and particularly impressive sign of aging It may, however, be widely independent of other signs of this process and must not be considered a causal or precipitating factor in general senescence The individually variable range of the endocrine glands participating in the aging process accounts for some of the symptoms and signs of old age, they determine its clinical picture to a certain extent but are themselves subject to the constitutional fate of aging The clinical picture of old age is brought about by the forces of constitution operating on tracks 1 2 and 3, the no- [illegible]
and 6 [illegible]
nism a[illegible] its interest mainly on the endocrine system as the part most readily accessible to therapeutic measures

H. Zondek[24] reports the case of a 36-year-old married woman with precocious senescence running in her family Five

of her sisters had gray hair at the age of 30 She had the appearance of a woman of 60, with her wrinkled, ashy pale, dry skin, gray hair, and bent body She showed advanced atrophy of the genital organs and breasts, had almost ceased menstruating, and the pubic and axillary hair had fallen out The patient resembled altogether a case of Simmonds' pituitary cachexia, all the more as her blood pressure was very low She died after an operation for gastric ulcer The autopsy revealed a marked general atrophy of all organs The ovaries were found to be almost completely fibrotic, connective tissue was increased to a moderate extent in the anterior pituitary and in the zona facsiculata of the adrenal cortex, the thyroid was found to be practically normal This case can be classified only as an instance of constitutional precocious senescence in which the clinical picture was largely determined by the share of the endocrine glands participating in the aging process

Sexual Differentiation —Sex and sexual differentiation of body and mind depend upon the chromosomal structure of the fertilized ovum Determination of sex does not mean merely the development of testicles or ovaries and the corresponding differentiation of the genital organs, but extends to all other characteristics of body and mind that are different in the two sexes Every cell originating from the fertilized ovum and the type of its function is male or female Long before puberty we are able to recognize a typical male or female temperament Experienced pediatricians are able to recognize boys and girls immediately after birth, solely on the basis of a somewhat different shape of the face and head Even before the differentiation of the gonadal anlage for testicles or ovaries can be determined microscopically, the sex of the embryo may be diagnosed from other physical characteristics

The hormones manufactured by the sex glands merely exert a protective and intensifying action upon the sex characteristics potentially determined by the chromosomal structure In man such an influence starts to be effective at the age of

puberty There is no indication, at any rate, of definite functional endocrine activity of the gonads before puberty,[4, 85] at least not in so far as hormonal stimulation of the sexual differentiation is concerned[87] As pointed out previously, differentiation of the various secondary sex characteristics does not occur simultaneously Each one has its characteristic time of manifestation The growth of a beard and of hair on chest and abdomen and the lowering of pitch of voice in the male, the development of breasts and the onset of menstruation in the female, take place in a regular order This fact indicates the importance of the constitutional reactivity to hormonal influences of the various effector organs

Sexual differentiation not infrequently fails to be complete *in every respect* There are men with more or less pronounced female characteristics, such as female measurements of the pelvis, female (eunuchoid) type of distribution of the subcutaneous adipose tissue or body hair, gynecomastia, high-pitched (eunuchoid) voice, female type of personality, and, more particularly, homosexuality The same holds true, mutatis mutandis, for women Draper[18] speaks of the "mosaic of androgyny" in this respect Thus far only secondary sex characteristics have been considered If the failure of sexual differentiation pertains to the primary sex characteristics, that is, to the genital organs, and if the type of fetal transformation of both the wolffian and müllerian ducts does not conform to the sex of the gonads, then the result is called *pseudohermaphroditism* If, finally, the gonads themselves are involved in such a failure of sexual differentiation and both testicular and ovarian tissue is to be found in one individual, the term *hermaphroditism* is used to designate the condition

Abnormalities of sex differentiation can arise (*a*) from an abnormal germ composition, that is, from an abnormally low prevalence of one sexual anlage over its antagonist, or (*b*) from a pathologic alteration of the endocrine system In the first case we are dealing with the *constitutional* (*genetic*, *zygotic*)

variety of intersexuality, brought about on tracks 1, 2, and 3 of our scheme, the second case represents the *hormonal* variety, produced on track 3

Certain types of tumors of the ovaries (arrhenoblastoma or andreoblastoma), of the adrenal cortex, or of the pituitary gland (Cushing's syndrome), are associated with abnormal sexual differentiation[25] Except where congenital tumors or hyperplasia of the adrenal cortex occurs in cases of pseudohermaphroditism, such endocrine diseases, developing at any period of life, may produce a change of the previous normal sexual differentiation A kind of transformation of sex characteristics is observed in arrhenoblastoma, cortico-adrenal tumors, or pituitary basophilism (Cushing's syndrome) The signs of such a transformation in females are development of generalized hypertrichosis, with a virile beard, enlargement of the clitoris, loss of menstruation and of normal sexual desire, sometimes development of homosexual tendencies, a lower pitched voice, and atrophy of the breasts In male adults adrenal cortical tumors occasionally were found to produce atrophy of the testes, with loss of sexual power, and gynecomastia, even leading to a watery secretion of the mammary glands Such a hormonal transformation of the sexual differentiation was demonstrated to be reversible by surgical removal of the particular tumor These observations in human beings are in full accord both with laboratory experiments carried out on animals and with recent experiences in patients treated with large doses of potent hormones

For a more thorough understanding of the role played by some endocrine glands with regard to sexual differentiation, several points may be mentioned briefly

(1) There is no absolute sex specificity in the stimulating action of the gonadal hormones upon sex characteristics In general, the stimulation extends to the sex characteristics, which, as well as the gonads themselves, are determined by the

chromosomal structure The gonadal hormones are intercalated as a sort of magnifier in the differentiating mechanism originating in the chromosomes Also, the sex hormones may exert a stimulating effect on both male and female sex characteristics to variable degrees in different species[28, 29] Even in the human species some estrogenic effects may be obtained by administration of male sex hormones[30] Gynecomastia was observed as an unusual by-product of administration of methyl testosterone[31] The hormone of the corpus luteum is known to produce androgenic affects[32, 33] Consequently Abarbanel et al[34] go as far as to reject such terms as "male sex hormone" or "female sex hormone," for each exerts both androgenic and gynecogenic activity

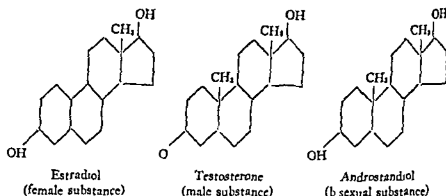
(2) That the suprarenal cortex must be manufacturing a sexotropic hormone, different from that which is indispensable for the maintenance of life, was a logical conclusion from clinical observations[3b, 35] In fact, androgenic[34] as well as gynecogenic[35, 36] effects were found to result from administration of various products obtained from the suprarenal cortex Desoxycorticosterone and the corpus luteum hormone exert similar effects in certain respects and can, in proper doses replace each other[36]

(3) There are numerous chemically related substances that have a more or less marked influence on the sex organs and secondary sex characteristics In so far as they have been recovered from certain organs of the body, they all derive from the sterol group * All hormonally active steroid substances were found to exert an influence on the vaginal epithelium[37] Butenandt[37] synthesized a substance, intimately related to both estrogenic and androgenic hormones, that induced estrus in castrated mice and opening of the vagina in infantile rats on the one hand, and growth of the comb in

* Stilbestrol is *not* a hormone, is chemically not related to the sex hormones and is not a sterol derivative, but induces powerful estrogenic activity

capons and of the vesicular glands in infantile male rats on the other The accompanying formula demonstrates the chemical relationship of these substances

The testicle of the bird contains large amounts of estrin even if there are only Leydig and Sertoli cells [38] R T Hill[39] discovered the remarkable fact that ovaries produce androgenic *hormone if exposed to low temperature, as effected by implantation* of ovarian substance in the ear of a rabbit He



Estradiol (female substance) | Testosterone (male substance) | Androstandiol (b sexual substance)

found, however, that the androgenic substance thus derived *from the ovaries is chemically not identical with that liberated* by the testes

From all these facts one may assume that a transformation of different sterol derivatives with various sexotropic activities takes place in the body under certain circumstances Trans *formation of male sex hormone into a substance with the action* of female hormone was first demonstrated by Steinach and Kun [40]

(4) *It may be considered an established fact today that* sexotropic hormones are not manufactured only by the sex glands and suprarenals, and that a transformation of such substances may also occur in organs other than those named Estrogenic substance can also be found in plants and bitumen Both estrogenic and androgenic hormones *may* be recovered from the urine of each sex, although in different ratios They are excreted also in the urine of castrates When testosterone

is administered to male[61] or female[62] castrates, excretion of increased amounts of both androgenic and estrogenic substances has been observed Symptoms and signs of gonadal insufficiency occurring after castration of aging males were found to be associated with only moderate changes in the urinary excretion of ketosteroids, estrogens, and gonadotropins[63] Hence it was concluded that a demonstration of sex hormones in the urine cannot be regarded as evidence of the functional capacity of the gonads[68, 69]

The liver seems to exert a marked influence on steroid hormones It inactivates the estrogenic hormone[70, 71] on the one hand, and has been found to produce estrogen from cholesterol on the other[71] The occurrence of testicular atrophy and gynecomastia in some cases of liver cirrhosis was related to the impairment of this inactivating influence of the liver upon estrogen More recent investigations of Cantarow et al[72] indicate that it may be the excretion of considerable amounts of estrogen through the bile, rather than inactivation by the liver, that explains the observed relations between liver and steroid hormones

(5) It is remarkable that thorough assays of the sex hormones excreted in the urine of patients afflicted with the cortico adrenal syndrome (interrenalism) have not added much to the understanding of its pathogenesis Marked masculinization in some cases of female interrenalism was found to be associated with excretion of extraordinarily large amounts of estrogen, and in a male case of interrenalism, considerable amounts of androgenic substance were excreted In other cases of the cortico-adrenal syndrome the expected reversal of the androgen estrogen ratio was indeed actually observed Hence the inference must be drawn that the tendency for sex inversion to occur in cases of interrenalism cannot be explained on the basis of excess production of the inverse sex hormone, since such an excess is not regularly found in these cases Although it may sound somewhat paradoxic, the inverse androgen-estrogen

ratio seems to be the consequence or at best a sign rather than the cause of the tendency to a transformation of sex characteristics. Such a tendency may be due either to a genetic (chromosomal) abnormality or to a disease of certain endocrine glands.

In 1927 the clinical facts known at that time induced me[66] to assume that the adrenal cortex supplies the body with a sexotropic hormone stimulating and intensifying the development and maintenance of the secondary sex characteristics in a fashion similar to that of the gonadal hormones. In contrast to the latter, however, the cortical (interrenal) sex hormone exerts a protective action upon the normally suppressed and latent characteristics of opposite sex. It enhances the capacity for penetration of the sex anlage that is concealed by the actually predominant one. The terms applied by geneticists to designate this type of prevalence and repression, respectively, are epistasis and hypostasis. As a matter of fact, absolute dominance or absolute recessiveness of a gene hardly exists. The prepotency of a gene over its fellow gene, called its allelomorph, is subject to individual variations. So also is the restraining power of one gene over another gene that is not its allelomorph, that is, whose relation to the prevalent gene is that of hypostasis to epistasis. The vast majority of intersexual individuals are genetic (zygotic), not endocrine in type. For the clinical diagnosis it is of prime importance to know at what age the abnormal sexual differentiation took place, and to know as well whether or not other members of the family have shown similar abnormalities. Most cases of hypertrichosis in women, for instance, are of this familial, that is, constitutional variety. The effector organ (B) is directly influenced by the abnormal sex anlage (A) on track 1 of figure 2.

According to this theory, the endocrine glands are interposed between A and B in so far as the gonads are acting as protectors and intensifiers of the actually prevailing sex anlage, whereas

the suprarenal cortex acts as promoter of the concealed sex anlage if excessive amounts of the particular cortical hormone are produced Therefore it is neither a generally masculinizing nor a generally feminizing hormone that is manufactured by the adrenal cortex The cortical sexotropic hormone depends in its action and effect on the chromosomal structure, the genetic sex anlage It is androgenic in females and may be gynecogenic in men This seems to be the underlying principle of its action, which has been fully recognized also by Schiller[45]

It is conceivable that the actual result of an interrenalism will depend on the interference of the genetic sex anlage with the transforming power of the cortical sexotropic hormone The normal male genetic structure seems to be more resistant to this transmuting influence than the female sex anlage This is to be concluded from the fact that cortico-adrenal tumors are less frequently associated with a transformation of sex characters in males than in females In male children affected with cortico-adrenal tumors, no inversion of the sex characteristics has been observed Sexual precocity without sex inversion in such cases is the result of interrenalism

It may be well to mention two facts reported in the medical literature of the last few years that strongly corroborate our theory In a case of Addison's disease in a 37-year-old man who was treated with massive doses of cortex hormone, the development of a veritable gynecomastia was observed[46] The gynecomastia subsided when the treatment was discontinued and recurred when the treatment was resumed There is another case of Addison's disease on record in which unilateral gynecomastia (see below) developed after treatment with cortical hormone[33] In a case of "feminism" in a male adult, unilateral suprarenalectomy performed by Broster[47] was followed by an improvement with regard to the abnormal sexual differentiation Incidentally, the excretion of androgenic substance in the urine was found to be even lower after

the operation than before, whereas the estrogen excretion remained unchanged.

Sex inversions produced by diseases of the endocrine system are brought about on track 3 of our scheme. Such diseases, inhering in tumors or hyperplasias, themselves depend on constitutional factors (A) operating on track 2. The different varieties of these endocrine sex inversions are caused by the following: (*a*) tumors of the ovaries originating from embryonic inclusions of tissue of testicular character (arrhenoblastoma), (*b*) tumors of the testicles originating from embryonic inclusions of tissue apparently having a female genic structure (teratoma, chorionepithelioma), one might consider both these groups a kind of delayed zygotic intersexuality or rudimentary hermaphroditism, (*c*) tumors, hyperplasia, or simple hyperfunction of the suprarenal cortex, (*d*) tumors of the anterior pituitary lobe, usually basophilic in type (Cushing's syndrome) and producing functional hyperactivity of the adrenal cortex by excessive production of corticotropic hormone. Cushing's syndrome must be considered as a "secondary interrenalism" induced by a primary selective overactivity of the pituitary gland. This concept of Cushing's syndrome, advocated since 1933,[48] seems to be almost generally accepted today.

Two varieties of localized intersexuality deserve particular attention from a practical point of view, that is, *homosexuality* and *gynecomastia*. It has become customary to consider these conditions as effects of an abnormal endocrine function.[49] Many facts discovered in the field of laboratory endocrinology were misleading in this respect. Administration of gonadal hormone of the opposite sex, with or without previous castration, may change and invert secondary sex characteristics, perhaps including the mental ones. Artificial production of mental sex inversion (homosexuality) in guinea pigs and rats was claimed to have been achieved by several experimenters. It became questionable, however, since Beach and his co-

workers[71] demonstrated masculine copulatory behavior in most intact and castrated female rats Only the feminine sexual pattern (receptivity) was dependent on the ovarian function, whereas the homosexual reaction occurred independent of ovarian hormones under appropriate conditions In normal male rats also a homosexual or bisexual behavior could be demonstrated by Beach[88]

The normal androgen-estrogen ratio was found to be altered in the urine of men affected with gynecomastia and in homosexuals as well It has been pointed out elsewhere[30] that the situation is far more complicated in human pathology than it seems to be from the standpoint of laboratory endocrinology The sex hormones manufactured by the gonads act as a kind of lubricant for those cerebral centers that represent the site of sexual urge In men at least the direction of this urge depends on the genic structure Two clinical experiences may serve as illustration of this fact

Kreuter[60] implanted testicles of a homosexual *in a man* who had been castrated on account of a bilateral tuberculosis of the testes The man had lost his former libido After the implantation his libido returned but did not show any trace of homosexual direction

Fischer[60] treated a eunuchoid by engrafting testicular tissue taken from a normal man The patient, who had previously lacked all libido, exhibited marked homosexual desires after the operation

In both cases, therefore, a stimulating action of the testicular graft could be observed, the direction of the sexual urge, however, did not depend on the character of the graft In other words, whether normal or homosexual libido *is incited* by testicular hormone depends on a factor other than the inciting hormone, it depends on the reactivity of the cerebral sex centers That this reactivity results from the genic structure of the individual is suggested by the fact that an *inverse* reactivity is frequently associated with physical signs characteristic of the

opposite sex Female body proportions, female type of hair distribution and of fat deposit, gynecomastia, high-pitched voice, etc , are not uncommon in male homosexuals Mutatis mutandis, the same holds true for female homosexuals The deviation of the androgen-estrogen ratio found in both homosexuals and persons with gynecomastia ranges among these various signs of abnormal sex differentiation It does not, however, account for either homosexuality or gynecomastia The reasons for it[80] are as follows· (a) The altered androgen-estrogen ratio is to be found statistically only, but does not characterize the individual homosexual This is in full accordance with what is observed as regards other physical signs of abnormal sexual differentiation in homosexuals (b) Wide variations are to be found in different assays on the same homosexual subject, chiefly in relation to the estrogen excretion; the subject is, however, just as homosexual when he excretes large amounts of estrogens and little androgen, as he is when the ratio is found to be the reverse (c) Efforts in treating homosexuality with endocrine procedures have failed so far The only success claimed by the advocates of this treatment[81] is the normalization of the androgen-estrogen ratio found in the urine The producer of the urine, however, has never been reported to have become normal This fact is therefore an invaluable corroboration of our concept of homosexuality It is worth mentioning in this connection that sexual desire in women was observed to be increased by implantation of pellets of testosterone, whereas it was diminished by pellets containing corpus luteum hormone [82]

Our concept of homosexuality does not rule out the cooperation of environmental and psychologic factors in its production, particularly during childhood The psychosexual differentiation is more liable to be influenced by experiences occurring before this differentiation becomes intensified and consolidated by hormonal action starting at puberal age If the actually prevailing sex anlage is not strong enough, it may be over-

thrown by psychologic and environmental factors that aid and enhance the development of the latent but suppressed mental tendency At all events there is no true homosexuality without a constitutional background

Only the genetic conception of homosexuality and gynecomastia can explain the fact that different varieties of intersexuality, both physical and mental, occur as a hereditary trait in certain families Homosexuality or gynecomastia are not the only deviations that may be found in a given family Such an event cannot be considered accidental[82] Berta Aschner[83] reported several instances of families in which various signs of intersexuality occurred together, or separate from one another, in different members of the same stock Such varieties of intersexuality were homosexuality, transvestitism, tendencies to occupations usually appropriate to the opposite sex, and more or less marked somatic features of abnormal sex differentiation As a matter of fact even true hermaphroditism, that is, ovotestis, has been reported in siblings[89] and pseudohermaphroditism in twins[90]

That gynecomastia cannot be explained merely from an endocrinologic viewpoint becomes obvious from the investigations of Wagenseil[92] on thirty-one Chinese eunuchs who were castrated during puberty or adolescence Seven among them, at ages between 53 and 74 years when they were examined, had gross gynecomastia Obviously it is not an excess or deficiency of a particular hormone, but a particular predisposition of certain individuals, that must be referred to in order to understand the fact that deprivation of the testicles resulted [illegible]

[illegible] all of the endocrine system The genetic structure of the respective cells of the end organ, that is, of the breasts, must account for their feminine behavior after castration The mere fact that unilateral gynecomastia occurs in certain individuals (p 100) gives proof of this

hypothesis Apert[93] reported a case of unilateral gynecomastia developing after castration This is an excellent illustration of the general biologic principle that has been discussed at *length previously: both the lack of the inhibiting influence of* the testicular hormone and the more or less female genetic breast structure (cf below) determine the development of gynecomastia In men with normal testicular function only a definite female genetic structure of the breasts will prevail over the inhibiting influence of the androgenic hormone and consequently result in gynecomastia Among men who have been deprived of their testicles, however, gynecomastia will develop even in those whose slightly female breast anlage was suppressed by the inhibiting action of the androgenic hormone before castration Gynecomastia has occasionally been observed in more than one member of a family [8a, 8b, 94, 95] Bonhoff reported an instance even of two first cousins both affected with unilateral gynecomastia

In the cases in which male eunuchoidism is associated with gynecomastia,[96] the gonadal hypoplasia itself may be the result of a genetic abnormality consisting of an abnormally *low prevalence of the male over the female, normally suppressed* sex anlage

A fundamental problem arises as to how cases of partial intersexuality conform to an abnormal chromosomal sex anlage What accounts for the fact that an abnormal genetic structure produces abnormal sexual differentiation only in limited portions of the organism, such as the brain, the breasts, or the larynx, with regard to the hair distribution, etc , in contrast to the sexual differentiation of the rest of the body? Two factors must be considered in this connection

(1) The genetic (zygotic) sex anlage determines whether the differentiation tends in the male or the female direction Each cell originating from the fertilized ovum by mitotic cell division is *possessed of the same genetic structure as the ovum* The actual sex anlage is the product of the interaction of both male

and female tendencies, resulting in a greater or lesser predominance of one or the other Since the degree of predominance is subject to variations dependent on time—among other factors involved—and even, as we pointed out above, on hormonal influences, it is conceivable that the threshold for expression of the latent sex anlage may be somewhat different in various cell groups of the body In other words, some parts of the body may manifest characteristics resulting from the expression of the concealed antagonist of the sex factor that is prevalent in the rest of the organism The mere existence of true hermaphroditism proves this

(2) There are racial differences concerning the expression of secondary sex characteristics Certain human races have very scanty beard and do not exhibit any sex differences so far as the distribution of body hair is concerned These facts are due to racial differences in the reactivity of cells and organs to formative impulses exerted by the sex anlage, and further enhanced by the respective sexotropic hormones The effect of the latter depends in turn on the racially different responsiveness of the effector organs Most interesting in this respect are the racial differences to be observed in the secondary sex characteristics of birds The Sebright cock, for instance, is hen feathered and does not have the long tail feathers characterizing roosters of other races Such long tail feathers grow, however, after castration of a Sebright rooster In other chicken races this trait is *suppressed* by the ovarian hormones and not influenced by the testicles, whereas in Sebrights both ovaries and testicles exert an inhibiting action upon this characteristic The racial difference inheres in the responsiveness of the end organ, that is, of the tail feathers, not in the function of the testicles

Whatever mechanism operates in the production of partial intersexuality in man, this intricate situation ...

... genetic

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In the cases in which male eunuchoidism is associated with gynecomastia,[96] the gonadal hypoplasia itself may be the result of a genetic abnormality consisting of an abnormally low prevalence of the male over the female, normally suppressed sex anlage

A fundamental problem arises as to how cases of partial intersexuality conform to an abnormal chromosomal sex anlage What accounts for the fact that an abnormal genetic structure produces abnormal sexual differentiation only in limited portions of the organism, such as the brain, the breasts, or the larynx, with regard to the hair distribution, etc, in contrast to the sexual differentiation of the rest of the body? Two factors must be considered in this connection

(1) The genetic (zygotic) sex anlage determines whether the differentiation tends in the male or the female direction Each cell originating from the fertilized ovum by mitotic cell division is possessed of the same genetic structure as the ovum The actual sex anlage is the product of the interaction of both male

In certain families several members may be suffering from different types of heart ailments, the heart being the constitutionally "weak spot" Emotional upsets will readily produce alterations of the heart action In such a family hyperthyroidism produces cardiac symptoms by predilection They may be almost the only manifestation of the disease if the hyperfunction of the thyroid is of mild degree, or they may be in the foreground of a more complex clinical picture if the hyperthyroidism becomes more severe Diarrhea and other gastro-intestinal disorders are often encountered as major symptoms of hyperthyroidism in a person whose gastro-intestinal tract is a locus minoris resistentiae Such a person has always had a delicate stomach and delicate intestines, these organs are upset by the slightest dietetic indiscretions, by various infections, and by psychic disturbances If an emotion such as that brought about by a school examination or by speaking in public causes diarrhea in an individual, it is not surprising that in this same individual diarrhea rather than cardiac symptoms initiates the clinical picture of hyper thyroidism

Whether a mild degree of hypothyroidism produces mental [illegible]

[illegible] it results in loss of hair, in an obstinate, chronic dermatosis, or in gain of weight, depends largely on the constitutional responsiveness of the various peripheral effector organs to an insufficient supply of thyroid hormone

Physiologic and artificial menopause are followed by an adjustment of the endocrine system to the new situation Hyperactivity of the anterior lobe of the pituitary gland is the outstanding consequence of this adjustment Such compensatory hyperpituitarism is evident from both morphologic and functional signs Increased output of pituitary gonadotropic hormone following the loss of ovarian function is understandable from a teleologic point of view However, increased

sex anlage, the endocrine system, and the responsiveness of the peripheral effector organs must be taken into consideration

b) CONSTITUTION AND ENDOCRINE SYMPTOMATOLOGY

In the preceding chapter the role of the endocrine system was discussed in so far as it works as mediator between constitutional tendencies and effector organs Referring to figure 2, we were interested in the detour represented by the endocrine system (C) acting on track 3 and influenced on track 2, we attempted to evaluate the share of this detour (tracks 2 and 3) and of the direct route (track 1) from the genetic constitution (A) to the peripheral effector organs (B) As a matter of fact, only some of the outstanding biologic processes such as growth, evolution, aging, and sexual differentiation have been discussed in detail Many others, such as the production of antibodies, the maintenance of the normal blood count by proper regulation of blood regeneration, the maintenance of blood pressure at a normal level, or the maintenance of normal body weight, are to be considered in the same way Here too the endocrine system functions in the realization of the constitutional capacity.

In the following section, the clinical picture of endocrine disorders, both constitutional and acquired, will be considered in so far as it is controlled by genetic factors In other words If B is acted upon by C on track 3, how is the clinical result modified by A acting upon B on track 1? We shall be rather brief in this discussion, as this problem has been considered in an earlier chapter We learned how the various clinical pictures of hyperthyroidism, hyperparathyroidism, or hyperinsulinism are brought about by variable responsiveness to excessive amounts of the respective hormones The threshold for toxic reaction to excessive amounts of certain endocrine products varies in different organs of a person according to their responsiveness, which in turn depends on both constitutional and environmental factors

the pituitary gland This possible accompaniment to the climacteric adjustment of the endocrine system must of course be verified by assays of corticotropic hormone

A fundamental factor must be taken into account The climacteric and the ensuing proper readjustment of the endocrine system are physiologic events In completely normal and well balanced women there are seldom climacteric symptoms of an intensity requiring medical attention If so, they indicate an individual inadequacy This, however, is produced largely by psychic factors "Change of life" as the supposed cause of various and even mortal diseases has become a powerful slogan promulgated by the lay press and the pharmaceutic industry Unfortunately the medical profession itself has become a victim of this slogan Doctors may involuntarily create rather than alleviate climacteric symptoms by asking about and suggesting them to a susceptible patient Lack of physiologic and psychologic understanding accounts for such events Furthermore, the slogan "change of life" is a simple and useful help for coping with many diagnostic and therapeutic difficulties It is the obvious consequence of misunderstanding of physiology if women are disturbed by the false idea that menopause means the onset of aging Aging goes on with or without the menstrual cycle The misconception, however, accounts for many nervous symptoms and for the depressive states so frequently encountered in climacterical women It is shortsighted to look upon menopausal melancholy as a simple and direct result of the lack of ovarian function A far more complicated mechanism must be considered For the therapeutic management of the "menopausal syndrome' the reader is referred to chapter 11 I feel that much could be accomplished to prevent the menopausal syndrome by intelligent counterpropaganda depriving the term 'change of life' of its disastrous implications

There has been much talking and writing about male climacteric If the term climacteric is used, as it should be, to desig-

output of thyrotropic pituitary hormone and of growth promoting hormone has also been found in climacteric women Whether or not hyperthyroidism results from this adjustment of the endocrine system depends on (a) the amount of excessive production of thyrotropic hormone, (b) the reactivity of the thyroid to this stimulus, and (c) the responsiveness of th peripheral effector organs, especially of the nervous systen to the increased amount of circulating thyroid hormone Therefore there are as a rule several causative factors tha in conjunction with the menopause produce the menopausa variety of hyperthyroidism [64] The following instructive case may serve as an illustration of this situation

A white woman, 46 years old, had dropped from 73 to 52 Kg in weight in three months following her menopause, in spite of normal appetite and normal food intake She complained of trembling, extreme nervousness, and palpitation, and was very emotional and cried frequently In the past few weeks the thyroid had become enlarged and there was a marked thrill over it. The pulse rate was 112 and the basal metabolic rate + 28 per cent

In this case of moderate hyperthyroidism, the etiologic factors were obviously the following (1) menopause (2) a constitutional hereditary predisposition to endocrine disorders in general and to thyroid hyperactivity in particular (both parents had been obese, the father weighing 90 Kg and the mother 97 Kg, the patient s daughter had been successfully operated upon for exophthalmic goiter three years before), (3) a psychic imbalance brought about by the death of a dearly loved brother, who had been nursed by the patient The brother s death coincided with her last menstrual period

If, however, the thyroid of a woman is functioning at its maximum capacity to fulfil the requirements of the organism, it may easily become overstrained and exhausted by the increased stimulation exerted upon it during the climacteric Hypothyroidism rather than hyperthyroidism may result from this situation The occasional growth of a rudimentary beard in climacteric women, perhaps also some varieties of overweight, arterial hypertension, hyperglycemia, and glycosuria occurring in the climacteric age may hypothetically be attributed to an excessive output of corticotropic hormone of

endocrine diseases result from the interference of the excess or lack of the particular hormone with the different responsiveness of the various effector organs to this hormonal alteration There is a threshold to be reached and a threshold not to be surpassed by a hormone if the maintenance of normal structure and function of the organism is to be secured These thresholds and the range between them apparently are not always the same in various organs The thresholds, as we have learned from clinical medicine, are determined by both constitutional (genotypical) and acquired (paratypical) factors

We meet with all types of cases, from full fledged deficiency, or extreme abundance of a hormone, to the *normal state—in* other words, from the classic clinical picture of an endocrine disease through its rudimentary, oligosymptomatic varieties to the normal Thus we may encounter patients who present but one or two signs of a hyper- or hypofunctioning gland A toxic goiter, for instance, may have been completely cured by surgery or other therapy, except for one symptom, such as a persisting tachycardia This may persist even if signs of a slight deficiency in thyroid hormone become apparent An obstinate constipation may respond to administration of thyroid substance in spite of the fact that no other definite signs of hypothyroidism were detected in the patient, and that thyroid substance cannot be considered a laxative Or we meet with isolated anomalies of body measurements, of hair growth, or of fat distribution that are readily taken for signs of an endocrine disorder

If, however, only a single sign limited to one organ suggests an abnormal supply, and all the rest of the body fails to show analogous signs, then it is not the endocrine function but the given organ that *must be considered abnormal* in so far as its requirement of the hormone differs from the requirement of all the rest of the organism In other words, it is not an *endocrine disorder* but an abnormal threshold of hormonal action in the particular organ that must be assumed This

nate the cessation of the gonadal activity at a definite period of life, with all the consequences brought about by such an elimination of the gonads from the endocrine system, there is little justification for using the term male climacteric The functional activity of the testicles slackens with advance in years There is, however, neither generally nor individually a definite age at which the testicles stop functioning as do the ovaries Flushes, vasomotor crises, and sudden attacks of perspiration characterize the menopause, these do not occur, however, in males The rise in concentration of gonadotropic pituitary hormone in the urine of women at the menopause has no counterpart in men with advance in years[88] There is not sufficient foundation for giving the whole gamut of neurasthenic complaints occurring in men between the ages of 45 and 60 the name of climacteric, just because a mental depression may be associated with sexual impotence

Whatever the special pathogenesis of menopausal symptoms and signs may be, the individual clinical picture is initiated by a more or less rapid cessation of the ovarian function and is completed by the constitutional reaction to this endocrine shift of the various organs, particularly of the central nervous system Constitutional tendencies involving the adaptive reactivity of some endocrine glands account for the changes in weight accompanying the climacteric It is estimated that about 25 per cent of all women gain considerably in weight with the onset of the menopause Those, however, who lose weight at this time, and represent the emaciated and dried-up type of senescence, are not infrequent I saw a woman of about 30 exhibiting this extremely lean variety of climacterical change after surgical removal of her ovaries, her mother showed the same type of reaction to physiologic menopause

Whether a eunuchoid or juvenile castrate will become obese, unusually tall, or neither, depends on the stock from which he originates and its constitutional tendencies

We learned how the various clinical pictures of the same

cell groups concerned must be assumed in such cases Such an autochthonous abnormality in the genetic structure is not uncommon in birds It accounts for what is known as gynandromorphism, that is, a mosaic like mixture of male and female characteristics in one individual We refer to what has been said about partial intersexuality on page 92 If modern writers on gynecomastia[46] complain that no satisfactory explanation has yet been offered for its unilateral appearance, it is because they consider only the endocrinologic and overlook the genetic (constitutional) aspect of the problem

There are rare cases of unilateral involvement in what is known as polyostotic fibrous dysplasia or osteodystrophia fibrosa Because of the clinical and roentgenologic similarity, such cases may be confused with fibrocystic ostitis due to hyperparathyroidism There is, however, no indication of hyperparathyroidism to be obtained from studies of both the calcium phosphorus metabolism and the parathyroid glands Moehlig and Schreiber,[47] in reporting an interesting instance of this condition, conclude rightly that there *may exist an* autochthonous peculiarity of the *mesenchymal* bone, and that the unilateral involvement of the skeleton may be accounted for by an "unbalanced chromosomal aberration" The latter term obviously denotes *what is* called "somatic mutation," that is, an alteration of the chromosomal structure occurring not in the germ cell but in one of the somatic cells during earliest embryonic life I refer to the publication of Moehlig and Schreiber because it exemplifies the need that constitutional pathology, including endocrinology, should be applied properly

According to this report, *the* patient's mother, both of the mother's parents, and two maternal aunts exhibited shortness of stature and premature loss of teeth This fact is presented as evidence of a 'familial d

self, a youngster of

pituitarism because

particular organ rather than an endocrine gland is abnormal and should be treated. I used the term *hormonal disharmony*[8b, 88] to designate those not uncommon pathologic conditions that are no less difficult to treat than to diagnose correctly. Our rich and complicated system of diagnostic labels is, and will always be, insufficient for the innumerable variations in clinical pictures that are produced by the innumerable different individual constitutions.

The failure of response of the end organ to some hormone has recently been emphasized by F. Albright et al.[91] They report cases of "pseudohypoparathyroidism" presenting the clinical picture and the metabolic changes of hypoparathyroidism but not responding to administration of parathyroid hormone in large amounts. The authors mention another probable example of failure of an end organ to respond normally to a physiologic hormonal stimulus, namely, patients with low metabolic rates without other evidence of hypothyroidism. It usually requires more thyroid hormone to elevate the metabolism to normal in these patients than is required in true hypothyroidism. If the conception is correct that such a hypometabolism is due to a lack of thyroid stimulation, and no other signs of thyroid deficiency are present, this condition fits exactly with our concept of hormonal disharmony.

The threshold of a hormonal action may be different even on the two sides of the body. In 1924[11] I published photographs of a 13 year old boy whose right breast had the appearance, shape, and consistency of the breast of an 18 year-old girl, and of an adult man who showed unilateral development of hair on the chest, which is another secondary sex characteristic. Both persons were otherwise normal. There can be but little doubt that such unilateral abnormalities of sex characteristics, like other unilateral signs of endocrine disorders, can be explained only by a difference in the responsiveness of the two sides of the body to the respective hormones. An autochthonous abnormality of the chromosomal apparatus of the

What is to be said about such a constitutional predisposition to endocrine diseases can be put very briefly, as it relates chiefly to the previously mentioned facts

We learned of the familial occurrence of pituitary dwarfism, obviously due to genetically determined malformations of the anterior pituitary lobe There are cases of congenital hypothyroidism due to a rudimentary development of the thyroid gland that may be represented merely by a thyroglossal cyst Such an imperfect development of the thyroid is, at least in the majority of cases, attributable to an abnormal anlage Cases of eunuchoidism occurring in several members of a family have been mentioned In the foregoing pages we met with instances of constitutional biologic inferiority of endo- [illegible] cases of Addison s disease [34,35] Whether or not the existence of a morphologic basis, such as hypoplasia, can be substantiated, the fact that both adrenals are affected by tuberculosis or some other infectious process bespeaks an individual predisposition of the glands—all the more so if we realize the rarity of tuberculosis localized in the suprarenal glands One variety of Addison s disease is due to an atrophic-cirrhotic process destroying the suprarenal glands Since such a condition has often been reported in several members of a family,[34,35,53] it is more than probable that an abiotrophic state of the adrenals reflects a constitutional background of the disease

In so far as endocrine diseases are produced by tumors originating from the glandular parenchyma, the constitutional predisposition is determined by two factors, the neoplastic tendency and the local factor This is but a particular instance of the general problem of constitutional predisposition in the formation of tumors, which will be discussed in a later portion of this book It may be well, however, to mention

absence of a beard and axillary hair, and feminine distribution of pubic hair. As a matter of fact, these signs in a boy 16 years of age cannot be considered as indicative of any endocrine disorder. There is likewise no justification for assuming on these grounds a hereditary dyspituitarism that would play "a significant role in producing a unilateral mesenchymal bone defect in the form of polyostotic fibrous dysplasia."[57]

What can be seen from the history of the case is a somewhat shattered genotypic structure of the stock, an accumulation of several genetic abnormalities—one of them represented by the high arched palate described in the patient—but not endocrine disorders. It is an instance of what we shall discuss in a later portion of this book as status degenerativus.

We reject the theory of an endocrine disorder playing a role in the pathogenesis of unilateral polyostotic fibrous dysplasia. It is to be denied all the more in the rare cases of unilateral achondroplasia or, as it should be called, hemichondrohypoplasia.[58] Such conditions range with unilateral formation of multiple chondromas impairing growth by involvement of the epiphyseal cartilages. This latter condition is known as Ollier's disease. All these unilateral abnormalities must be attributed to unilateral disorders of the chromosome set. This in turn is understandable only as somatic mutation of genes occurring in the earliest stages of embryonic development. That such somatic mutations occur at all is in my opinion less amazing than that they are encountered as extreme rarities. It may be well to recall what has been said in a previous chapter about constitutional biologic inferiority of one side of the human body (p. 56).

c) RELATION OF CONSTITUTION TO ENDOCRINE MORBIDITY

The problem we are about to discuss next is the following: How do diseases of the endocrine system depend on particular constitutional anlagen? In terms of figure 2, what is the role of A acting upon C on track 2 in producing actual diseases of C?

The same holds true for the consequences of nutritional deficiencies, particularly vitamin deficiencies It is known that chronically underfed animals exhibit endocrine disorders dependent chiefly on a depression of the pituitary gland[59] Certain clinical features occurring in sprue, as well as in anorexia nervosa, may be attributed to a reversible impairment of the pituitary function[60] So far as anorexia nervosa is concerned, this interpretation has recently been fully confirmed[61] The clinical picture in many cases of curable anorexia is difficult to distinguish from that presented by the fatal Simmonds' pituitary cachexia, which is due to an anatomic destruction of the anterior pituitary lobe Only a careful study of the patient's personality and the demonstration of an actual nutritional deficiency preceding the first symptoms and signs of hypopituitarism enable us to differentiate these conditions The result of the treatment is the final proof

What we are interested in here is the fact that not all persons chronically underfed, owing either to disturbed intestinal absorption, as in sprue, or to a mental disorder, exhibit the clinical picture of anterior pituitary lobe insufficiency It seems unnecessary to refer to the various manifestations of vitamin deficiency that have been studied so thoroughly in the last few years I have seen many of them in the frequently undernourished Negro population of Louisiana, but I did not see the syndrome of pituitary cachexia among these people And the nutritional deficiency of those suffering from some kind of avitaminosis is not limited to one or more of the vitamins but is as a rule a general caloric undernutrition Hence it is to be concluded that another factor, the reactivity of the pituitary and other glands to nutritional deficiency, must be taken into consideration

In so far as nervous (mental) anorexia is concerned, a more intricate pathogenic mechanism than that of a simple depression of the pituitary function by undernutrition must be taken into account The latter represents only one operative factor

cases of multiplicity of tumors reported in the literature, all affecting the endocrine system in its various parts. Multiple adenomas of the pancreas, parathyroids, and pituitary were described in several cases.[84] Such observations bring to the fore the fact that the constitutional biologic inferiority of the endocrine system acts as a localizing factor in the etiology of tumors. It has been pointed out previously that certain endocrine glands may become "weak spots" in so far as they are involved in the sphere of action of an abnormal gene complex ruling the growth function or the storage of fat. Thus it may happen that tumors, cysts, or other diseases of endocrine glands encountered in persons exhibiting constitutional disorders of growth or of fat accumulation, should sometimes be considered the consequence rather than the cause of such disorders.[85b, 86]

Observations suggesting a constitutional biologic inferiority of the thyroid gland have been mentioned previously. There is a long list of authors who studied the inheritance of simple goiter.[83] Of 128 patients with simple goiter or hyperthyroidism, 36.7 per cent had relatives affected with the same condition, whereas only 11.3 per cent of control persons with normal thyroid had relatives suffering from simple goiter or hyperthyroidism.[83] These figures, obtained among patients in Vienna (Austria), cannot as a matter of fact be applied to other regions. They are, however, significant and prove that a hereditary, that is, a constitutional factor is operative in the etiology of goiter and thyroid hyperfunction. The occurrence of hyperthyroidism in several members of a family is not unusual.

Whether or not traumatic injuries, such as might occur to the parathyroids during a strumectomy or to the testicles during a hernioplasty, are followed by symptoms and signs of impaired function of the respective glands, seems to depend not merely on the degree of the injury but also on the innate degree of perfection of these glands.

V

THE INTEGRATIVE SYSTEMS OF INDIVIDUAL CONSTITUTION—II

2 The Nervous System, Psychosomatic Medicine

The nervous system acts as one of the integrative systems of the individual constitution, in so far as its autonomic part regulates the function of practically all organs and tissues, including the endocrine glands Whereas the regulation of bodily structures and functions by the endocrine system is chiefly of an enduring, so to speak tonic type, the nervous regulation serves for momentary, rapid adaptation of the body to various situations and stimuli Since the endocrine activity is subject to nervous regulation, and the latter in turn is largely controlled by hormones, the most perfect system of mutual check and balance is secured in the constitution of an average person The autonomic nervous system is also the moderator between mind and body, since it transmits emotions to the somatic sphere either directly or through the mediation of the endocrine system, particularly the suprarenals Emotions, however, are influenced by the activity of endocrine glands, such as the thyroid, the gonads, the pituitary the pancreatic islets, and the parathyroids Let us recall for instance the psychic manifestations of hypoglycemia or the mood and behavior of a patient suffering from hyperthyroidism or tetany

Another is the direct influence of mental processes upon pituitary activity[41] M Schur and C V Medvei tried to approach this problem from both the physical and the psychologic side[42] We believe it a most interesting problem, requiring the diagnostic and therapeutic methods of what is known today as psychosomatic medicine

Whether or not bacterial infections such as typhoid fever, acute rheumatic fever, dysentery, acute streptococcic tonsillitis, and others, induce hyperactivity of the thyroid, and whether or not symptoms and signs of a functional depression of the suprarenals accompany scarlet fever and other acute infectious diseases, depends at least partially on the constitution of the respective glands The same holds true for the individually different effects of menopause and pregnancy upon the endocrine system The biologic worth and responsiveness of the glands account for the fact that some pregnant women develop tetany and others acromegalic features Both endocrine alterations disappear with the termination of pregnancy Some women, however, exhibit signs of temporary exhaustion of the pituitary function after delivery They may show more or less definite symptoms of pituitary insufficiency for varying lengths of time Pregnancy can be considered the grand functional test of the biologic worth of the endocrine system

sympathetic and sympathetic systems, affecting in various degrees various parts of the autonomic nervous system This was pointed out in 1912[1] and has since been corroborated by many authorities[2] It does not matter whether this constitutional state is termed neuropathic constitution,[2] vegetative (autonomic) stigmatization,[3] neurocirculatory asthenia, or otherwise What matters is in my opinion the fact that the excessive reactivity of the autonomic nervous system is as a rule indicative of a more general hyperirritability of the nervous system, including its highest cortical functions Therefore it seems that the term "neuropathic constitution" fits the situation best Persons of this type may or may not complain of various symptoms, they may or may not require medical attention They are, however, predisposed to diseases, called functional or neurotic, that are induced by physical or mental strain, emotional conflicts, or somatic diseases of any kind It is the psychosomatic personality with its emotional instability, its excessive, inadequate, and untimely reactions, and its maladjustment to various situations, that creates the individual predisposition to functional disorders and neurotic complexes

Alvarez speaks of "constitutional inadequacy"[4] and feels that nothing or very little can be done about it It is perfectly true [illegible]

stitut [illegible]

does [illegible] situation It is too pessimistic to consider the condition of such patients hopeless They need intelligent medical attention, they need medical guidance, and if they do not find it where they are entitled to ask for it, they inevitably become the clients of chiropractors, osteopaths, Christian Scientists, and what not. These leaders of cult medicine and quacks of different *varieties certainly* do not know *more* about human nature than scholarly, trained physicians *They know*, however, sometimes better than the latter, how to handle constitutionally inadequate, superstitious, and suggestible per-

a) NEUROPATHIC CONSTITUTION

There are great individual differences in the reactivity and irritability of the nervous system, both cerebrospinal and autonomic The variable liveliness of nervous reactions extends from the highest cortical functions, such as association of ideas and emotions, to the spinal reflexes and actions of the autonomic nervous system For those who wish to have objective evidence of such individual differences, psychologic and neurologic tests are available

In the domain of the autonomic system, functional tests have been used in observing the different reactions to definite amounts of epinephrine, pilocarpine, or atropine There are, however, some less inconvenient and simpler clinical tests for the responsiveness of the parasympathetic system Marked respiratory arrhythmia, considerable slowing down of the pulse rate by bending forward (Erben's sign) or by pressure on the eyeballs (Aschner Dagnini sign), indicate hyperirritability of the parasympathetic nervous system, at least of some parts of this system These clinical tests frequently furnish more valuable information about a patient's constitution than many complicated and time consuming laboratory methods Even simpler is the evidence of vasomotor hyperirritability (flushing of the upper part of the chest and of the neck, dermographia), of moist and frequently cold hands, and of excessive perspiration in the axillae All these signs are incontestable indicators of exaggerated irritability of the autonomic system This may or may not be the underlying background of a patient's complaints, it is, however, always an invaluable criterium of a patient's constitutional type and of his reactions to various stimuli and situations, both physical and psychic

The concept of *vagotonia* and *sympathicotonia* characterizing individual personality types is theoretic and ingenious rather than practical and real There is no such thing as strict vagotonia or sympathicotonia There are, however, hyperirritability and excessive responsiveness of both the para-

culatory asthenia In cases of this kind another member of the same stock may show anxiety or compulsion neurosis, hysteria, some kind of addiction, or criminal psychopathy All these various types of functional disorders of the nervous system, pertaining to both the mental and somatic spheres, arise from such neuropathic constitution This is the functional manifestation of the constitutional biologic inferiority of the nervous system

The consequences of a psychic shock depend on the individual constitution, as is illustrated by Murri's studies[3] on the survivors of the earthquake of Messina No one of them failed to show mental disorders in the first few days following the catastrophe Some days later the majority of the survivors were adjusted and became mentally normal again After several months only those representing the constitutional neuropathic type were still suffering

Hysterical reactions such as crying spells, mutism, or convulsions may occur after a severe psychic blow, even in normal persons, without any subsequent neurosis Bismarck, for instance was reported to have had a crying spell after the decisive defeat of the Austrians by the Prussians in 1866, and he was neither hysterical nor otherwise psychopathic We mention these facts because they demonstrate various types of functional nervous diseases that are but exaggerations, prolongations, and complications of reactions inherent in the average nervous system The more hyperreactive the given nervous system is, the more trite and insignificant may be the psychic or physical shock that precipitates a neurosis

A recent issue of the *British Medical Journal** contained a report to the Medical Research Council on fainting in blood donors It presents painstaking statistics concerning sex, age, occupation nourishment, and other factors, it does not, however consider the constitutional make up of the habitual fainters It can be assumed without elaborate statistics that

* Feb. 26, 1944 p 279

sonalities They apply practical, instinctive psychology unhampered by scientific knowledge and ethical inhibitions They will prosper, and never completely disappear, so long as persons with neuropathic constitution exist, and so long as medical practice is considered merely applied medical science and not also an intricate art

The genotypical character of what we have called neuropathic constitution is suggested by the fact of its duration throughout life and by the family history Several members of the same family may exhibit various manifestations of the same neuropathic disposition Such manifestations may be limited to the aforementioned signs of hyperexcitability of the autonomic nervous system, with or without exaggerated deep reflexes, but without actual complaints One member of the family may fall ill with symptoms diagnosed as neurasthenia or as neurocirculatory asthenia The synonymous terms "effort syndrome" and "soldier's heart" indicate that this condition occurs more frequently and becomes more interesting and important during or before a war At these times the hardships and emotional upsets of military service act as provocative factors in transmuting a constitutional "inadequacy" into an actual disease Yet there is nothing particular or specific about this syndrome occurring in neuropathic soldiers How little known the true—constitutional—nature of this condition is may be inferred from the fact that the case of a 45-year old soldier was considered worth being reported in the *Journal of the American Medical Association*[24] The man had been discharged from military service during the first world war by reason of "neurocirculatory asthenia," his pulse in standing position being 144, in recumbent position 92, he had to be discharged from the army again during the second world war for the same reason, with exactly the same symptoms and signs The man could make a fair adjustment to the life of a farmer, but not to that of a soldier Nothing else could be expected, considering the constitutional basis of neurocir-

These well known facts have been misinterpreted in two opposite ways Some authors are inclined to regard hyper thyroidism as the actual cause of all types of nervous hyper irritability and believe that what is called neurocirculatory asthenia represents only a variety of hyperthyroidism[5]

Another group of authors considers exophthalamic goiter the result of a primary nervous imbalance[6] The real situation is as follows The thyroid gland is intercalated into the autonomic nervous system as a kind of multiplier and magnifier It is supplied with parasympathetic nerve fibers from the laryn geal nerves and with sympathetic fibers running in the walls of the thyroid arteries More recent investigations have re vealed an extraordinary abundance of fine nerve fibers forming a very dense reticulum around each thyroid cell Fine fibrils originating from this reticulum enter into the cell plasma it self and form a continuous syncytial network throughout the whole thyroid gland[7] Physiologists have taught us that these nerves influence the output of the hormone from the gland and there is no doubt therefore that pathologic alter ations of this regulatory nervous apparatus have repercussions upon the thyroid function Although we have no informa tion about the location of the brain centers representing the point of origin of these regulating autonomic nerves of the thyroid we are justified in referring to them in a particular group of cases of hyperthyroidism

In the last few years there have been observations of cases of encephalitis and particularly of epidemic encephalitis that exhibited more or less marked symptoms of hyperthyroidism The unanimous explanation has been based on the assumption of a cerebral origin of this thyroid hyperactivity The centers regulating the thyroid function must be involved in such cases by the encephalitic process In cases exhibiting hyper thyroidism after carbon monoxide poisoning a toxic lesion of these centers has been assumed to be the cause of the thyroid hyperfunction[8]

they belong to the large group of neuropathic persons with autonomic nervous imbalance.

There are strains of goats and rats exhibiting all the signs of constitutional nervousness. A loud noise or sudden surprise induces rigidity or loss of consciousness in such goats After a few seconds of having been "scared stiff," they regain normal use of their limbs Flocks of these neuropathic goats are kept in Texas and Tennessee A similar condition is known to occur in certain strains of rats They go *into convulsions*, have abnormal muscular twitching, or urinate or defecate when faced with problems that they cannot solve Exposure to glaring light or unpleasant noises make them feel uneasy. The differences in the nervous responsiveness of various races of horses and dogs are well known.

b) THE ROLE OF THE THYROID

In discussing the nature and manifestations of "nervousness" we have to take into consideration the important role played by the *thyroid gland* as a regulator of nervous activity.

Hyperirritability of the entire nervous system is a characteristic finding in both neuroses and hyperthyroidism Restlessness and emotional instability are indicators of such hypersensitiveness in the higher cerebral centers Lively deep reflexes, tremor, increased vasomotor reactivity, heightened excitability *of both the sympathetic and parasympathetic systems* in their various parts, with its long train of consequences, are common signs encountered in both neurotics and hyperthyroids Similar effects can be produced experimentally in animals by poisoning them with thyroid hormone Palpitation, headache, pains all over the body, insomnia, fatigue and exhaustion, anxiety, and other symptoms due to a disturbed function of the autonomic system, are common complaints of hyperthyroid *patients* These symptoms may, however, be equally well observed in the neurotic where there is no evidence of an involvement of the thyroid

These well known facts have been misinterpreted in two opposite ways Some authors are inclined to regard hyperthyroidism as the actual cause of all types of nervous hyperirritability, and believe that what is called neurocirculatory asthenia represents only a variety of hyperthyroidism [5]

Another group of authors considers exophthalamic goiter the result of a primary nervous imbalance [6] The real situation is as follows The thyroid gland is intercalated into the autonomic nervous system as a kind of multiplier and magnifier It is supplied with parasympathetic nerve fibers from the laryngeal nerves and with sympathetic fibers running in the walls of the thyro[illegible] arteries More recen[illegible]

[illegible] each thyroid cell Fine fibrils originating from this reticulum enter into the cell plasma itself and form a continuous syncytial network throughout the whole thyroid gland [7] Physiologists have taught us that these nerves influence the output of the hormone from the gland, and there is no doubt, therefore, that pathologic alterations of this regulatory nervous apparatus have repercussions upon the thyroid function Although we have no information about the location of the brain centers representing the point of origin of these regulating autonomic nerves of the thyroid, we are justified in referring to them in a particular group of cases of hyperthyroidism

In the last few years, there have been observations of cases of encephalitis, and particularly of epidemic encephalitis, that exhibited more or less marked symptoms of hyperthyroidism The unanimous explanation has been based on the assumption of a cerebral origin of this thyroid hyperactivity The centers regulating the thyroid function must be involved, in such cases, by the encephalitic process In cases exhibiting hyperthyroidism after carbon monoxide poisoning, a toxic lesion of these centers has been assumed to be the cause of the thyroid hyperfunction [8]

Much better known and much more frequently observed are cases of hyperthyroidism initiated by psychic shock or by repeated *strong emotions There is almost complete unanimity* on this point

The fact that primary cerebral alterations of a functional character can induce hyperthyroidism leads to the conclusion that certain centers of the brain may be the point of origin of hyperthyroidism, whether they be involved by an organic process such as encephalitis or carbon monoxide poisoning *or by a functional psychic alteration As a matter of fact* only predisposed persons will develop hyperthyroidism under the latter circumstances The assumption of an individual predisposition is necessary in order to explain why only a small number of persons react with hyperthyroidism to the alteration of the supposed cerebral centers A thorough examination of such patients usually reveals signs of such a predisposition operating together with the nervous alteration in the pathogenesis of hyperthyroidism In one case the onset of the menopause, in another an acute or chronic infectious process in still another an obvious familial tendency to thyroid disease may cooperate with the psychic shock in producing hyperthyroidism

To recognize these cases with a psychic factor operative in their etiology is of practical importance, because it determines whether, and to what degree psychotherapeutic treatment is required in the individual case If the question arises as to whether or not psychotherapy, or even psychoanalysis, is of any value *in hyperthyroidism, the answer must be Patients* with an obvious psychologic background need consideration of this fact, and the results of any therapeutic methods directed to the glandular hyperactivity will be greatly improved if this psychotherapeutic factor in the treatment is not neglected

The term psychotherapy, however, is by no means to be identified with psychoanalysis or with any other special *method of* psychiatric treatment In the cases referred to,

some "minor psychotherapy," applied by the family physician or the internist, will usually be sufficient

On the other hand, it must be realized that the thyroid hormone raises the irritability of the nervous system and acts somewhat like a lubricant of the nervous machine In such a way a vicious cycle may readily be established, involving both the nervous system and the thyroid and originating in either one These theoretic considerations, and the study of a particular group of patients, supplied the reasons for separating this group from other varieties of both neuroses and hyperthyroid states and for calling such cases *thyroid neuroses*[1] The diagnosis *thyreoneurosis* or *neurothyreosis*—according to the dominance of one or the other factor—was used to label cases presenting the features of neurosis together with signs of mild hyperthyroidism It frequently seems futile to search for the primary origin of the disorder, and to decide in which part of the chain represented by the nervous system and the interposed thyroid gland the alteration started

As a matter of fact it is somewhat arbitrary to establish sharp limits between neuropathic constitution, hyperthyroid constitution, and thyreoneurosis The term *hyperthyroid constitution* is to be used for those constitutionally nervous individuals who present signs of slightly hyperactive thyroid, as indicated by a tendency to tachycardia and excessive perspiration, fine tremor of the fingers when separated, leanness contrasting with the amount of food taken, vasomotor and emotional instability, and in particular slightly elevated basal metabolic rate Wide palpebral fissures glaring eyes, and frequently the intermittent appearance of a white strip of conjunctiva [illegible]

sign)

sign is [illegible] by sudden retractions of the upper eyelids occurring during a conversation with these always jittery individuals As long as such a condition is compatible with health and does not induce the subject to ask for medical at

tention, it may be called hyperthyroid constitution. This constitutional anomaly is not to be considered an actual disease, since it represents a permanent and inherent characteristic feature of the individual personality. It is, however, the factor obviously predisposing to a thyreoneurosis if its possessor is exposed to detrimental environmental or intrinsic conditions, either physical, mental, or both. It stands to reason that it is not sufficient to decide whether or not hyperthyroidism exists in a patient. The conscientious physician attempts to comprehend the individual in his whole psychosomatic personality. He tries to know the type and origin of the hyperthyroid condition, because its successful treatment depends largely on such knowledge.

c) OTHER NERVOUS DISORDERS OF ENDOCRINE SECRETION

In the previously mentioned condition of *anorexia nervosa*, we learned about the intimate relation between a psychoneurotic state and the functional activity of the pituitary gland It was emphasized that undernutrition, with the subsequent vitamin deficiency, accounts for only a part of the pathogenetic mechanism. The functional depression of the pituitary activity seems to be brought about in part also by a direct nervous influence. Psychoanalytic studies of such cases reveal an intricate mental process operative in inducing an anterior lobe insufficiency.[9] From a psychoanalytic point of view, it is the struggle between the destructive death instinct and the self-preservative life instinct that has to be considered the underlying mechanism of anorexia nervosa. The depression of the pituitary activity is held to be the somatic expression of such a struggle.

It is known that not only disorders of the menstrual cycle but even more extended hormonal disorders may occasionally result from psychic emotions. I remember a patient with the clinical picture of imaginary pregnancy who exhibited amenorrhea, marked protrusion of the abdomen by reason of meteor-

istic distention of the intestines, and enlargement of the breasts with discharge of some serous fluid from the nipples Luetzenkirchen[10] reported the case of a 29 year old divorced woman who developed the typical syndrome of adiposogenital dystrophy associated with diabetes insipidus after having suffered a severe psychic blow She recovered completely after regaining happiness in another marriage

Such experiences bespeak a nervous control of the pituitary function Suggestive clinical hints may sometimes be gathered far ahead of the relevant physiologic and anatomic knowledge We are not lacking however, in experimental proofs of nervous control of the pituitary gland In rabbits, matura [illegible] the intercourse the rabbit s pituitary is removed ovulation and subsequent formation of a corpus luteum fail to occur Depletion in follicle stimulating hormone of the pituitary gland was found immediately following sexual intercourse. These facts demonstrate the nervous control of discharge of the pituitary hormone After the air raids in London delayed menstruation was frequently observed as an effect of emotional shock Endometrial biopsies revealed arrest of the developmental cycle of the endometrium brought about by inhibition of the release of gonadotropic pituitary hormone via the autonomic nervous system[11]

In clinical practice we meet with hormonal disorders produced by an *altered mechanism* of *discharge* rather than by altered manufacture of the given hormone At least this mechanism of discharge, which is adapted to the requirement of the body by nervous control, is *often* involved in diseases of endocrine glands Let us recall the paroxysmal crises of arterial hypertension, with their characteristic clinical picture, occurring in cases of chromaffin tumor, or the hypoglycemic crises associated with tumors of the Langerhans islets Ex

cessive production of adrenalin in the first, of insulin in the latter tumors, takes place without any doubt What accounts, however, for the paroxysmal character of the hormonal intoxication?

The sympathetic system promotes the discharge of adrenalin, the parasympathetic that of insulin As I pointed out in collaboration with Leriche,[11] *it may not be purely accidental that* most of the hypertensive crises in cases of chromaffin tumor occur in the early morning after the night's rest During sleep the parasympathetic system is dominant (Bauer)[1]; in the morning the sympathetic awakes, so to speak, and stimulates the release of excessive amounts of adrenalin accumulated in the hyperactive chromaffin tissue

The reactive discharge of insulin induced by an increasing blood sugar level is brought about at least partially through the mediation of a stimulation of the vagus center Laboratory experiments on animals demonstrated that true emotion as well as sham rage causes a discharge over both the vago insular and the sympathetico adrenal system, with a predominance of the latter under normal conditions[12] This predominance, however, can be altered by denervation of the adrenals Without taking into consideration this nervous control of insulin discharge from the pancreatic islets, we should be at a loss to understand why paroxysmal crises of hypoglycemia are characteristic of islet tumors

Reference to the aforementioned mechanism throws light upon a group of patients who may be diagnosed as neurotics or psychoneurotics by the neurologist or psychiatrist and as endocrinopaths as well by the endocrinologist These persons are *representative of neuropathic constitution,* they are generally of the lean, asthenic type and complain of various neurotic symptoms They have normal or low but still normal fasting blood sugar level A thorough examination, however, may reveal an exaggerated tendency to reactive hypoglycemia following alimentary hyperglycemia Abnormally low blood

sugar levels can be found from two to five hours after the onset of a routine glucose tolerance test, and may or may not be associated with definite symptoms of hypoglycemia. Spontaneous imperative craving for sweets may occasionally be suggestive of this condition. These persons do not necessarily have any tumor or other organic disease of the pancreatic islets or of their antagonists, such as the adrenals, the pituitary, or the thyroid. They are unquestionably neurotics whose nervous hyperirritability happens chiefly to bear upon the mechanism controlling carbohydrate metabolism. Excessive discharge of insulin brought about by unbalanced nervous impulses seems to account for some of the clinical symptoms. It is not the hypoglycemia alone, however, that explains the patient's condition, hypoglycemia is the consequence rather than the cause of the actual disorder, although it may modify the clinical picture. Both the neuropsychiatrist and the endocrinologist are right in their diagnoses, but only intelligent comprehension of the patient's psychosomatic personality affords the key to successful therapy. Those patients are in need of treatment by an all around physician rather than by a specialist who limits his interest and knowledge to one part of the body only.

d) ORGAN NEUROSES

The same principle is valid in all kinds of "organ neuroses." Functional alterations of various organs arising from unbalanced nervous regulation may involve the activity of both smooth muscles and glands, or may pertain to sensitivity of various organs [illegible]

ity, or of spastic [illegible]

cardia. These are all signs produced either as reflex phenomena by autochthonous organic disease, or by primary alteration of the nervous regulation. This in turn may be altered by an organic lesion of nervous centers—one may recall the visceral symptomatology of tabes or the appearance of peptic ulcer with or without hematemesis in certain cerebral le-

sions—or by a functional disorder of the nervous system arising from a neuropathic constitution or from an endocrine disorder One rarely fails to detect more or less intricate mental processes, conscious, subconscious, or unconscious ones, that are instrumental behind the scene in the production and maintenance of the actual organ neurosis of a predisposed neuropathic individual As a matter of fact the term organ neuroses should be applied only to those functional alterations of organs that arise from primary functional disorders of their nervous control The constitutional background of an organ neurosis should be duly appreciated Occasional emotional upsets, mental conflicts, psychic complexes, hardly spare anybody nowadays Yet only in constitutionally neuropathic persons do they become pathogenic and produce the clinical picture of organ neuroses

The localization and type of *organ neurosis is determined* both by the biologic inferiority of an organ and the kind of psychic complex that may be operative in the background *Nervous indigestion of different varieties occurs more* frequently in families exhibiting other signs of a constitutional weakness of the digestive tract, such as peptic ulcer or cancer *of the stomach Cardiac neuroses preferably affect members* of families haunted by organic heart diseases This has been emphasized in a previous part of this book Thorough psychologic *analysis, which need not be orthodox psychoanalysis* in Freud's sense, frequently furnishes the clue to the special clinical picture of an organ neurosis One example of a not altogether common *neurosis may illustrate this situation*

A 26-year-old married woman had been suffering occasionally since her tenth year from pain in the back, shoulders, neck, and hips, particularly on sitting or lying in the same position for a long period During the past eight weeks, backache and muscular pain in the scapular region had become excruciating, occurring even at night and preventing the patient from falling asleep *She had to get up and take a hot shower to get relief* In spite of negative X ray pictures she was told that she had incipient tuberculosis of

the spine Another orthopedic surgeon diagnosed her condition as "static postural imbalance associated with (*a*) valgus of both ankles and flatness of both longitudinal and metatarsal arches (*b*) forward flexion of the head at the level of the seventh cervical vertebra, with an increased dorsal curve and a compensatory increase in lumbar hollow

The latter orthopedic authority was right in his statement, but overlooked the fact that a psychic rather than a static postural imbalance accounted for the disease The first man did not realize the disastrous psychologic effect of his errone ous statement A third man specializing in the treatment of "rheumatic diseases" was equally unsuccessful in treating the patient's "rheumatism"

The physical examination of the patient and laboratory tests gave nega tive results except for the finding of a tenderness of the involved muscles. The elucidation of the problem was obtained from the knowledge of the patient's personality She was a spoiled only child of a very nervous and emotional mother Both the mother and the father were recognized stage artists They were divorced The patient's complaints in childhood were attributed to rapid growth and poor posture. She started studying ballet dancing and acrobatics but had to discontinue her studies because of nausea and dizziness She frequently vomited but never experienced any pain during her work The patient had married a renowned artist. He was just about to divorce her She had always been a poor sleeper and had occasional crying spells

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pat[illegible] from childhood on Her wish to become a dancer and acrobat resulted from the well known tendency to overcom pensate her biologic inferiority *She failed*, not because of an incapacity of the weak organ but because of interfering manifestations of her neuropathic personality other than those pertaining to the locomotor system The emotional distress resulting from her marriage acted as an enhancing and activat ing factor in the production of her actual neurotic condition The situation was explained to the patient in several confer

ences in a sympathetic and reassuring manner She lost her pain, at least temporarily

Conditions of this kind are also known as "psychalgia" and may readily be conceived as a variety of organ neuroses, that is, as sensory neuroses of the muscular system The threshold of sensory impulses originating in any portion whatsoever in the periphery varies greatly with the mental state of the individual Anxious attention concentrated upon a particular spot of the body may lower the threshold of afferent impulses arising from this spot and may render them more or less unpleasant sensations There are hyperthyroid patients with pulse rates of 80 suffering a great deal from palpitation, whereas others with pulse rates of 140 are not aware of a tachycardia A healthy person may feel considerable pain in a muscle group that has become acutely strained for lack of previous training Whatever the mechanism of such muscle pain, the sensation of pain is transmitted by nerve fibers It is conceivable therefore that under certain circumstances a painful sensation may be experienced although no adequate stimulus is operative Hyperirritability of sensory nerves and centers, enhanced by the aforementioned mental factors, seems to suffice to elicit such a psychalgia

e) THE NERVOUS FACTOR IN ANGINA PECTORIS

Should not the same considerations be applied to the problem of angina pectoris? The current theory of angina pectoris explains the agonizing pain as a result of ischemia of the heart muscle It seems to me that this theory cannot accord with the manifestations in all varieties of angina pectoris We do not attempt here to discuss the pros and cons of the theory according to which certain symptoms are to be considered as aortalgic rather than as cardiac pain It is my belief that such a concept is correct with regard to the substernal pain, experienced with or without the characteristic radiation that occurs during muscular effort in patients with hypertension or

aortitis What counts here is the fact that all kinds of pain are transmitted by afferent nerves supplying both the heart muscle and the adventitia of the aorta, no matter what mechanism may account for their stimulation during an attack of angina pectoris These nerves and their cerebral centers deserve more attention than is usually given to them The threshold of a painful sensation transmitted from the heart or from the aorta is subject to the same general rule as that in all other painful sensations Several factors influence this threshold: (*a*) the pre-existent degree of nervous excitability; (*b*) lowering of the threshold by psychic factors and particularly by anxious expectation of such a pain; (*c*) lowering of the threshold by repeated attacks of the same pain, according to the physiologic principle of facilitation

The strict distinction between a true and a false (spurious) angina does not cover the facts, if the latter term is used for cases of angina pectoris that are not produced by organic lesions of the coronary arteries, the heart muscle, or the aorta Such an organic lesion may exist, and an attack of angina may nevertheless be due to excessive irritability of the respective afferent nerves and their centers The practical importance of this concept is paramount This is demonstrated by the following observed case, which is a self explanatory illustration of the value of applied constitutional pathology in the consideration of a patient's whole personality, including both the physical and the psychic aspect

A 48-year-old successful business man experienced substernal pain during muscular exertion for the first time at the age of 41 There was no anxiety connected with the pain, and the patient was able to continue walking or working despite substernal pressure His cond[illegible]

[illegible] spite of many treatments for syphilis the serum reaction remained unchanged The cerebrospinal fluid,

however, was found to be normal When I saw the patient for the first time, he had been kept in bed for three months and had been given another series of bismuth injections The attacks of angina pectoris, however, had become more and more frequent and annoying I was asked whether intravenous administration of neoarsphenamine could be tried without danger

The attacks were described as "crowdedness" in the upper epigastrium, followed by a squeezing sensation, with subsequent numbness in both arms, in the left more than in the right, and in the jaw. There was no anxiety, and no immobilization of the patient during the attacks On the contrary, he felt better getting up, and could frequently "walk off" slight attacks Severe attacks occurred only at night, sometimes even four or five times in succession, and were usually preceded by heavy dreams The patient sometimes took 8 or more tablets of nitroglycerin, 1/100 grain, during a single night, and took it prophylactically before sexual intercourse Physical examination did not reveal any abnormality except for a somewhat accentuated but not ringing second aortic sound The blood pressure was found to be remarkably unstable, it varied between 140/90 and 90/65 Immediately after rising it would drop suddenly for a short while before reaching the former level Once it was found to drop to 65 systolic after the patient had arisen from recumbent position but it very quickly regained the former value of 110/80 This shifting of blood pressure was never accompanied by any subjective sensations or discomfort X rays did not show any definite abnormality of the chest or abdomen Repeated electrocardiograms were either quite normal or showed inconstantly a negative T wave not only in the third but also in the second lead All laboratory tests gave normal results except for the positive Wassermann reaction

The first impression, confirming the diagnosis of the patient's physician, was soon rejected for the following reasons (*a*) There was no evidence of syphilis of the aorta or of the heart muscle to account for the attacks of angina pectoris The positive serum reaction indicated merely that the man had once been infected with syphilis (*b*) If the attacks of angina pectoris had been produced by a syphilitic lesion, some signs of aortitis or myocardial damage should have been present seven years after the onset of the disease, all the more so since the disease had become worse in spite of antisyphilitic treatment (*c*) The pain was not immobilizing the patient but was relieved by movement, furthermore, it was not accompanied by anxiety (*d*) Study of the patient's personality and of the

attacks gave decided suggestion of a psychoneurotic background playing an important role in the etiology of the disease

The patient was a tall, strong man of muscular type He was Jewish, and had served as a flyer stationed at an American airfield during the first world war until he suffered concussion of the brain in an accident He had been tense since his boyhood He practiced all kinds of sports but was conscious of the contrast between his hero-like appearance and a real, carefully hidden cowardice He was particularly worried by his constantly strongly positive Wassermann, and consulted many authorities all over the country He was very anxious to keep his syphilitic infection secret. *He had made a* fortune by successful enterprises as a young man, was bankrupt in 1927, but became a rich man again soon after After the bankruptcy he had to spend several weeks in a sanatorium for 'nervous breakdown' He had divorced his first wife and was not at all happy with the second He had *numerous* domestic troubles and many difficulties *with his employees* He was always tormented by bad dreams One of these dreams was significant and recurred [illegible]

and *medicines* for backache, headache, spasms, indigestion, hay fever, and what not He was very delicate concerning his diet and the slightest *current* of air Our patient was disgusted with this type of person but was *afraid* that he himself, the 'strong healthy man,' was going to become very much like his friend The dream was as follows *The patient went for a walk in* the forest with his little son Suddenly he had to fight a big lion *in order* to protect his son, who was standing behind him *It was a struggle for life* and death He woke up frightened, with a sensation of 'crowdedness,' and had to take nitroglycerin His friend's name happened to be Lyon

I watched the patient during several of his frequent attacks of angina pectoris His blood pressure rose *from* 10 to 25 mm of mercury systolic and by 10 mm diastolic for the short duration of the pain Psychic factors ruled both the provocation *of* attacks and their prevention Slight emotions, insignificant as they might be, induced attacks Two puffs of a cigarette offered to him by a friend provoked pain immediately—obviously not because of a deleterious effect of nicotine, but because he had been told to avoid smoking and was afraid of the consequences of smoking He was advised that his

former syphilitic infection had nothing to do with his angina *and that aminophylline injected intravenously would dilate his* coronary arteries, keep them dilated, and prevent spasms Several injections were effective, but only for twenty-four hours each For the first time in three months the patient had a good night's rest without taking any nitroglycerin Then the aminophylline was replaced by physiologic saline solution, without the patient's knowledge, and proved to be just as effective

The problem of using placebos and "fooling" patients will be discussed later What counts here is the fact that *the main* pathogenic factor in the production of angina pectoris in this particular case was the excessive irritability of the nerves carrying or of the centers receiving afferent impulses from both the heart and aorta Mental processes and facilitation by repeated stimulation lowered the threshold of excitability of these nerves and their centers Neuropathic constitution was the background making possible the development of such an ailment Continuous antisyphilitic treatment was *not only* unsuccessful *but did actual psychic harm to the patient The same is true* as regards keeping an *active man in bed for three months* The only successful method of treatment was a psychologic one The use of aminophylline and its replacement by saline were, as a matter of fact, psychotherapy, although not officially declared to be such, and although not one of the standardized methods It was what I used to call "larvated or disguised psychotherapy" adapted to the individual case

We considered the above described nervous psychic mechanism the "*main*" *pathogenic factor This was* because the cooperation of a "*minor*" one could not be ruled out Whether or not the patient had an insignificant subclinical syphilitic process in the aorta, or, as seemed more probable, some arteriosclerotic changes in his coronary arteries, could not then be proved nor disproved Who has not known of patients suffering for years from angina pectoris diagnosed as angina

spuria, who eventually died of a vera? There is no such thing as a sharp borderline between a true and a false angina Each case has to be studied individually, and its treatment must be adapted according to the proportion in which organic and functional nervous factors participate in its etiology

Through the courtesy of Dr Fred Modern I learned about the ultimate fate of our patient I had lost sight of him through the imprudence of a physician

After having been treated unsuccessfully by irradiation of the supra renals, he was finally subjected to a thoracocervical sympathectomy under avertin anesthesia in a university clinic in the Middle West. He continued having anginal pain after the operation, developed progressive jaundice on the twenty third postoperative day, and died of subacute yellow atrophy of the liver The autopsy revealed arteriosclerotic changes in the coronary vessels.

The objective of our profession is not merely to detect the slightest organic alteration of the body and to pass in the dissecting room before the pathologist as the supreme judge The objective must be to help the patient, to relieve his pain, to diminish his suffering and to prolong his life, no matter what method of treatment proves successful

Objective signs of organic disease must not delude one with regard to a nervous and mental component accounting for at least a part of the clinical picture The presence of both organic and functional factors cooperating in the production of clinical pictures is almost the rule Organic changes may act as determining factors *in the* localization of psychogenic symptoms They may indicate a biologic inferiority of the organ itself, constitutional and/or acquired in type, predisposing to a particular type of a neurosis

f) FACILITATION AND CONDITIONED REFLEXES

Coughing and vomiting, for instance, are physiologic reflexes incited as defense *mechanisms* under certain circumstances Cough is a regular symptom of pertussis or of a catarrhal in

fection of the upper respiratory tract Individuals of neuropathic constitution may develop an automatization of this defense reflex that sometimes outlasts the original disease for a considerable length of time This is due to excessive facilitation of the reflex by both the nervous hyperexcitability and the hypochondriac tendency to undue, apprehensive attention *to this symptom Cough, having been originally a symp*tom of an organic disease, has become a symptom of a neurosis

Vomiting occurs as a physiologic defense reflex in acute indigestion or in pyloric stenosis It occurs just as frequently, however, as a reflex phenomenon elicited as a "useless" adjunct in peptic ulcer without pyloric stenosis, in gallbladder disease, appendicitis, diseases of the urinary or genital tract, etc The greater the excitability of the nervous system, the greater the emotional upset of the patient caused by such an organic disease, and the greater his apprehension, the more readily will vomiting accompany the uproar of the abdominal autonomic nervous system brought about by the organic disease If a patient with a peptic ulcer at the lesser curvature, or harboring concretions in the gallbladder, gives vomiting as one of his chief complaints, we record it as a symptom of his organic disease Yet the frequency and type of vomiting and its association with other symptoms and signs may furnish valuable information about the patient's personality Such a patient is suffering from an organic disease The clinical pic*ture of this disease, however, is molded by his personality,* and a neurotic component superimposed upon and mingled with the organic disorder should not be overlooked It frequently supplies the clue for a successful treatment E G Billings,[11] discussing "repercussions of personality disorders" and especially the case of a peptic ulcer in a constitutional neuropath, makes the statement "Treating the lad as a patient with peptic ulcer proved ineffectual Treating him as a personality with peptic ulcer as a complication was effective"

Dietetic indiscretions may occasionally do harm by their psy-

chologic rather than by their physiologic or biochemical effect Apprehensive self reproach for having eaten or done something forbidden and supposed to be injurious may occasionally be detected as the true inciting factor in certain symptoms [14] Many psychoneurotic disorders are to be attributed to conditioned reflexes Such conditioned reflexes develop readily, the more sensitive the nervous system is, and the more the individual personality takes part emotionally in the situation that conditioned the reflex I had under my care a famous actress who complained of vomiting before playing a certain part on the stage The mechanism of this vomitus was revealed to be a conditioned reflex The actress had been playing this particular part abroad with great success when she was surprised by an unwelcome pregnancy accompanied by physiologic vomitus This experience was charged with such an emotion that it became the starting point of a conditioned reflex Each time the patient had to play the same part the reflex was initiated

g) THE NERVOUS FACTOR IN ALLERGY

There has been much discussion of psychic factors in allergy There are several mechanisms involved

(1) Allergic conditions may give rise to conditioned reflexes The frequently quoted experience of Trousseau is an excellent illustration A woman suffered from bronchial asthma due to allergy to roses She suffered an asthmatic attack when she saw a rose in Trousseau's buttonhole, the rose happened to be an artificial one made of paper The optic impression of a rose so frequently coincided with the pathogenic action of the antigen that it eventually induced an asthmatic attack on its own account without any action of the antigen

(2) Allergic conditions are supposed to be brought about by antigen antibody reactions taking place in smooth muscles

the particular antibody

the threshold of respon

siveness to stimuli of the involved tissues Independently of allergic sensitization and desensitization, these tissues respond more readily to nervous stimuli By the principle of facilitation, nervous stimuli may become effective in such tissues, whereas they would not be effective had the previous allergic reactions not occurred The role of an originally immunologic reaction may be taken over by a nervous reaction This is all the more true if the reaction is charged with a great deal of apprehensive emotion Spastic contractions of the bronchial muscles, of the intestines, of the blood vessels, may first be allergic in type and later become nervous and psychic in origin

It stands to reason that a full understanding of this mechanism is paramount Successful desensitization of a patient may remove his allergy and yet not cure his disease Careful study of the patient's psychosomatic personality sometimes seems to be more important than the application of cutaneous tests These routine tests indicate whether or not an allergic condition exists in the skin, they do not indicate much about whether a similar condition is present in the bronchi, the nasal mucosa, the intestines, etc Different allergens may be operative in different organs "Psychic allergy," *if I may misuse this* term, is at least as frequent as true allergy in the immunologic sense of the word There are no "allergens" available for testing when we have to deal with an emotional hypersensitivity to a mother in law, a superior, a business companion, a teacher, and the like And yet the clinical picture of such a psychoneurosis may be much the same as that of an allergic condition It may be that of bronchial asthma, angioneurotic edema, urticaria, migraine, intestinal or biliary spasms, etc

h) PSYCHOSOMATIC MEDICINE

From our previous discussion the paramount importance of what is called psychosomatic medicine is self-evident Furthermore, it is self-evident that psychosomatic medicine is by

no means a new specialty of medicine, properly, it ought to be medicine itself Medicine that does not take a psychosomatic approach to the patient's ailment is poor medicine It is the duty of the internist or general practitioner to appraise the share of both the physical and the psychic portion of a clinical picture It is bad practice to adhere too closely to the routine labels of diseases Diagnosis should comprise the recognition of the mechanism operative in the production of the patient's symptoms and signs This means more than the choice of the most nearly correct label for marking a disease, it means also a full comprehension of the patient's personality and constitution

With regard to the organic physical or functional nervous problem and psychologic character of a case, not so frequently an "either/or but most often an "as well as" applies in dealing with internal diseases other than acute bacterial infections or acute poisonings From this realization one would conclude that the proper management of the cases under discussion would lie in the hands of the internist I am in full accord with Houston[15] concerning his statement "Diagnosis and treatment cannot be successfully divorced and must always go *hand in hand* ' The creation of diagnosticians as a specialty group is in my opinion one of the outgrowths of the attempt of modern routine medicine to accumulate as many tests as possible on a patient Austrian[16] has said

> Certainly, a sufficiently complete diagnostic survey should be made of each condition until its *nature is clear*, but the routine performance of needless tests indicates a lack of skilful observation and thinking, dulls clinical acumen penalizes patients wastes time and material, and gives the public an incorrect view of the cost of sound medical care

What counts even more than this is the too frequently disastrous effect on the patient's mental balance produced by all these tests which are not always correctly interpreted although correctly *performed* Hypochondriac tendencies may result from such painstaking work done by a diagnostician

I fully agree with Alvarez,[17] who recognizes very clearly the harm done to the patient by this routine practice of medicine. In the words of this author,

> One of the curses of medicine today is our tendency to worry before the patient about a 1+ Wassermann reaction, a basal metabolic rate of −15, a blood sugar of 120, a blood pressure of 100, an exaggerated haustration of the colonic shadow, two fecaliths in the appendix, a slightly slowed emptying of the gallbladder, or an inverted T wave in lead III. Unless the young graduate in medicine soon acquires the wisdom to disregard these things, and above all to keep quiet about them, he becomes a fertile breeder of neuroses.

Psychosomatic medicine is properly defined as

> That part of medicine which is concerned with an appraisal of both the emotional and the physical mechanisms involved in the disease processes of the individual patient, with particular emphasis on the influence that these two factors exert on each other, and on the individual as a whole.

"To the medical practitioner there is nothing new about psychosomatic medicine" (Caughey).[18] In fact it is as old as medicine itself, and the ancient Greeks knew more about it than do many modern young physicians. Why has it met with so much interest in the last few years? Why has a new term been invoked for an old notion, and why are books and periodicals dedicated to the subject? Because the modern trend toward considering medicine merely as applied exact science threatened to choke this old notion because the human mind has been included in the curriculum of medical schools only in so far as obvious derangement of it calls for the attention of a psychiatrist, and not with regard to its participation in somatic ailments. Medical practitioners knew about psychosomatic medicine only what they had gathered from personal experiences. Those who were deficient in the art of medicine never learned from their own practice what had been withheld from them in medical schools. The resurrection of psychosomatic medicine is a reaction to the outgrowths of modern laboratory medicine, which overlooks the patient behind the

files of reported tests It attempts to shift as much as possible of the mental processes from the realm of an intuitive art into that of an exact science

However, the way in which this is done by some modern investigators in the field of psychosomatic medicine may well turn out to be a blind alley It is my conviction that the endeavors to correlate certain psychologic personality patterns with definite somatic morbid predispositions will be a failure Repressed emotional tension, inhibited aggressive hostility ("chronic rage"), and similar psychologic features are by no means specific or characteristic of individuals who develop essential hypertension,[25] peptic ulcer, or any of many other somatic diseases[22] arising from or frequently associated with a particular constitutional neuropathic background We can hardly subscribe to Draper's[23] interpretation of clutching ulcer pains ('often called hunger pains by laymen")—namely, that they "represent a residual fear, repressed since infancy, that the maternal source of food and protection will be cut off' It is not conceivably possible to assume that a particular "type of personality susceptible to Parkinson's disease"[24] exists

After several sporadic forerunners, a systematic survey—*Psychogenesis and Psychotherapy of Somatic Symptoms*—was published in Vienna in 1925 by O Schwarz, in collaboration with other experts[19] Ten years later there was published in this country the excellent review of H Flanders Dunbar,[27] *Emotions and Bodily Changes*, compiling all our knowledge on the subject In 1930 a report was published on the results of psychotherapy systematically applied to a selected group of patients visiting the medical department of the Policlinic Hospital in Vienna[20] This represented the first time, to my knowledge, that systematic psychotherapy was made available to "medical" patients consulting the medical outpatient department of a hospital The usefulness of such an organization is being confirmed by introduction of the system in large and

recognized medical institutions in this country[18] The question whether psychotherapy should be made available to such patients in the medical department itself, or through close collaboration of the medical and the psychiatric department as is done in Denver, is of minor importance What does matter is that the internist should not lose sight of the patient should know where, when, and how psychotherapy may be of value, and should be familiar with the technic of what we may call "minor psychotherapy" as one of the most important tools in his therapeutic armament

How should medical schools provide their students with this skill? As was pointed out some seventeen years ago,[21] this type of knowledge is to be acquired not so much through courses in psychology or psychiatry as by watching great clinical teachers at the patient's bedside The tremendous influence of the *teacher's personality upon the student's future behavior* in approaching a clinical problem can hardly be overrated In fact, with the modern trend to mechanization and standardization of nearly all occupations, this relation seems to be fading away, and the famous name of the great clinical teacher is being supplanted by the renowned name of the school

j) PSYCHOTHERAPY

We do not attempt here to discuss the methods and technic of psychotherapy[28] It may be well, however, just to touch on a few items It seems to me that more stress should be laid upon re education of a patient on psychosynthesis rather than psychoanalysis, on readjusting him for the future rather than on digging into his past It is the striving more than the achievement that makes a man happy and makes him fit

Minor psychotherapy is frequently applied in a disguised form The administration of tonics and vitamins is largely such a disguised psychotherapy There is much controversy

over whether benevolent "white lies" told to the patient conform with professional honesty In my opinion they do As a matter of fact, the administration of placebos is the commonest variety of medical lie, and Houston[15] and Cabot[22] believe that the majority of medicines and drugs are nothing else but disguised placebos I agree with Houston[15] regarding his statement that psychotherapy will gain in precision and vigor if employed without placebos I do not agree with him, however, if he considers drugs a poor camouflage for psychotherapy, and if he thinks that the telling of a lie probably never is good treatment The academically correct point of view is not always applicable in practice for many reasons If Mrs X feels pepped up a few minutes after having taken a thyroid tablet, of what use would it be to destroy this illusion? The most instructive instance of the tremendous therapeutic value of a "benevolent lie" is a case from my former medical service in Vienna published with kindred observations[23]

> A 26-year-old man had to be completely castrated because of a bilateral tuberculosis of the testes. The surgeon implanted a sham testicle made of paraffin and the patient believed all his life that he had lost only one testis. In [illegible] fe [illegible] p[illegible] h [illegible] h[illegible] ary tuberculosis.

In may be questionable whether or not the surgeon acted honestly by using what Houston calls "fraud therapy" There is however, no question that the practitioner was not only a good surgeon but also a great physician It would be hypocrisy to deny the justifiability of such a fraud The excellent results of the university pediatric clinic in Vienna with children suffering from various types of neuroses are obtained exclusively by means of placebos This disguised psychotherapy includes the mothers In other words the mothers

too are made to believe in the therapeutic value of the placebos As a matter of fact, it is most pertinent by whom, when, and how a placebo is prescribed The personality of the physician is in this respect just as important as the personality of the patient "Watch your word," should be a maxim never to be forgotten by a physician His word is a therapeutic instrument no less powerful and no less dangerous than the surgeon's scalpel This very important fact has been stressed since 1925[29] and was recently fully recognized by Hurst[30]

VI

CLASSIFICATION OF NORMAL AND ABNORMAL CONSTITUTION

1 Criteria for Classification

There are as many different constitutions as there are individuals, except in the case of identical twins, who have the same set of chromosomes in common It stands to reason therefore that any effort to classify normal human constitutions and to establish a system of constitutional types must be more or less arbitrary and subject to general agreement

It is somewhat different if we take into consideration persons with definite constitutional abnormalities In the early part of this book we met with groups of individuals who can readily be separated from others because they have in common certain constitutional features, such as constitutional biologic inferiority of an organ, partial infantilism or senilism, endocrine stigmatization or neuropathic temperament There is nothing arbitrary about differentiating a large group of Negroes exhibiting the sickle cell trait This group is characterized by a morphologic anomaly of the red blood corpuscles that in the majority of cases is nothing but a harmless constitutional deviation, an internal cosmetic defect, so to speak—constituting however, a definite predisposing factor in relation to a serious disease occurring at a rate of from 1 5 to 10 in 100 carriers of this constitutional trait[1] If any constitutional anomaly should be spoken of as marking a "disease race"

it is sicklemia, which fits in connection with this term used first by Bartel[2] and adopted by Draper

Many criteria have been used for classification of human constitutions, both normal and pathologic The simplest classifications used by laymen cover the facts better than some of the "scientific" systems There is no objection to the distinction between tall and short, stout and lean, strong and weak, dark and blond, bright and sluggish persons Classification, however, that uses the muscular tonus (Tandler)[3] or the tonus of each part of the autonomic nervous system (Eppinger and Hess)[4] as a criterion is open to criticism With regard to the latter it has previously been pointed out that pure vagotonia and sympathicotonia hardly exist, and that signs of increased excitability of both parts of the autonomic *nervous system, varying in its different branches,* are the usual companions of neuropathic constitution

2 Endocrine Types

The attempts to classify human constitutions from an endocrinologic standpoint have gained much popularity Each structural and functional constitutional trait is subject to individual variation within the limits of health and of what rightfully may be called normal This is valid also so far as the functional value and arrangement of the endocrine glands are concerned In a previous chapter we became acquainted with what is called the *hyperthyroid* constitution The opposite type is represented by the *hypothyroid* constitution Persons of the latter type are short and stocky, have short and broad necks, short, wide and puffy hands and fingers tend to overweight, do not readily perspire, and are of phlegmatic, sluggish temperament

There are persons who may be regarded as having *hypoparathyroid* constitutions High irritability of peripheral nerves, as tested by a markedly positive Chvostek sign (twitching of the facial muscles produced by tapping on the facial nerve), oc

casional dragging sensations, numbness and stiffness of the extremities, occurrence of spasmophilic manifestations in infancy and of tetanic symptoms during pregnancy, are the chief indicators of this constitutional type

There are individuals whose general make up calls to mind acromegaly Such a person is characterized by a coarse skeleton, prominent, big jaw, protruding supra-orbital arches and zygomatic bones, a broad and plump or unusually long and prominent nose, thick, protruding lips, and big hands This habitus, unlike that of the true acromegalic, however, does not change, being fully developed by the time the individual reaches adult age Other members of his family may show the same general appearance A mild excess in production of the anterior pituitary growth promoting hormone, or an exaggerated response of the effector organs to this hormone, accounts for this type, and it may be said to represent *acromegaloid* constitution As a matter of fact, individuals of this type seem to be preferred candidates for true acromegaly due to a tumor of the anterior pituitary lobe

According to the same principles of classification, *hypopituitary*, *hypogenital*, *hypo and hyperadrenal* constitutions have been distinguished It must be emphasized, however, that exuberant fantasy rather than critical scientific appraisal of facts was frequently at work as far as details of these various constitutional types are concerned It is, for instance, not justifiable to correlate certain types of dentition with peculiarities of the endocrine system Our own studies did not corroborate the assumption of some endocrinologists that hypoplastic upper lateral incisors, particularly strong canines, or large upper median incisors, are in any way indicative of definite endocrine types [4] There is no such thing as a "hypogenital hand," as has been claimed by some authorities Long and slender hands and fingers with acrocyanosis occur in many persons without any signs of hypogenitalism Hypertrichosis in females is with relatively far greater frequency a hereditary

trait pertaining to the peripheral organ itself rather than to the suprarenal glands There is no such thing either as a pituitary, ovarian, or thyroid type of distribution of subcutaneous adipose tissue[5]

3 Status Thymolymphaticus

What was described in 1889 by A Paltauf[2] as status thymolymphaticus is of historical rather than of actual interest today This author and his followers drew attention to the fact that persons who had died suddenly and unexpectedly, without adequate reason, frequently were found to have large thymus and hyperplastic lymphatic tissue wherever such tissue may be found in the body Death of such type may occur after or even before local anesthesia preceding a minor dental or nasal operation, or may befall an individual in a swimming pool or after a slight injury or a psychic emotion From experiences gathered in the first world war it was learned that in healthy young men killed in action the thymus was larger than had previously been considered normal It was shown that any fatal disease produces a marked involution of thymic tissue It became clear too that the large thymus found in many suicides had to be considered as indicative of perfect health rather than of abnormal constitution Nevertheless there exist rare cases of abnormally large thymus, with or without a more or less marked hyperplasia of the lymphatic tissue, that may deserve the term status thymolymphaticus However, it should be borne in mind that this diagnosis of abnormal constitutional state should not be made except with great caution Furthermore, to our knowledge the hyperplastic thymus itself does not directly account for an otherwise inexplicable sudden death

It was found that a status thymicus need not be associated with a status lymphaticus, and vice versa—in other words, that hyperplasia may involve either the thymus or the lymphatic tissue or both Furthermore, these states were found to be

sometimes combined with hypoplasia (narrowness) of the aorta,[n n] or of the whole vascular system, with hypoplasia of the heart, the chromaffin tissue, and/or the gonads, and finally with various kinds of malformations and constitutional deviations These statements induced J Bartel in 1908 to speak of a *status hypoplasticus* This term is intended to indicate a hypoplastic state involving a tendency to premature wear of various organs, followed by replacement of the atrophying parenchymatous tissue by proliferating connective tissue Thus the concept of status hypoplasticus became a sort of resurrection of what older authors had called "fibrous diathesis"[1]

If we had to reject the hypothesis of a "mors thymica," that is, a sudden, otherwise not explained death following insignificant events and induced by a functional alteration of the thymus, what else could account for such incidents? Such deaths were reported to have occurred in several members of a family, and French authors therefore spoke of a *diathèse de mort subite* Neither the hypoplasia of the circulatory system nor that of the chromaffin tissue is a sufficient explanation Acute swelling of the brain (*akute Hirnschwellung*) was assumed to be the causal factor, it seems, however, that ventricular fibrillation unleashed in certain predisposed persons by various otherwise insignificant physical or mental factors may account for such events (H E Hering)[2]

An important contribution to this question has been made by *Raab*[n] He had opportunity to investigate such a case of sudden death in a young athlete and found excessive amounts of an epinephrine like substance in the heart muscle Acute poisoning with the epinephrine like substance accounted in Raab's opinion for ventricular fibrillation and sudden death Another similar case corroborated this theory[54]

Recently such sudden death was reported as having occurred in identical twins who were outstanding athletes[n] One of the brothers was autopsied and was found to have a hyperplastic thymus and narrowness of the descending aorta

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improved by some kind of surgical treatment These indi viduals are on the contrary occasionally victims of surgery, are operated upon over and over again, and develop what we pre viously mentioned as 'surgicophilia'

On the other hand some of the symptoms and signs occa sionally complained of by these persons may be caused by abnormal distribution of the circulating blood Such symp toms and signs are the tendency to orthostatic tachycardia, to dizziness and to fainting which may be facilitated by an abnormal retention of blood in the abdominal viscera owing to the enteroptosis and to the insufficient tonus and insufficient respiratory contractions of the abdominal muscles (Wencke bach)[2] A proper corset is the best aid in combating these dis orders Other complaints of asthenic persons, such as pain in the back or abnormal fatigue may be attributed to poor de velopment of the muscles and to slackness of ligaments An cient Greek physicians distinguished persons with 'status laxus' from those with 'status strictus'—which actually is nothing but the modern distinction between asthenic and hypersthenic types

5 Neuropathic Constitution

Neuropathic constitution with its repercussion on various bodily functions the individual behavior, and the reaction to organic diseases, has been discussed previously There is no need for further comment Just one point may be stressed here To recognize a constitutional neuropath it is invaluable to take the patient's history oneself and to watch him as he tells his story, to notice how he does it, his emotions, his words, and his movements This is sometimes of greater diagnostic importance than the physical examination and all available tests together

Primary dysmenorrhea is almost invariably a symptom of neuropath...

o

However, he furthermore had coronary arteriosclerosis and hydronephrosis affecting the left kidney. As a matter of fact, *coronary arteriosclerosis with subsequent thrombosis may* cause an unexpected sudden death even in young individuals.[illegible]

4 ASTHENIC CONSTITUTION

In 1907, B. Stiller distinguished a group of persons characterized by a particular habitus and by certain functional, psychologic, and clinical features as well. He described these people as possessing *asthenic* constitution. The general make up of such an individual is well known. He is slender, frequently tall, has a long thin neck, a long, flat, and narrow chest with a narrow upper thoracic aperture. Prominent second ribs, acute epigastric angle, small abdomen, drooping shoulders, and winglike, widely separated shoulder blades are characteristic. There is often a slight cervicodorsal kyphosis, the extremities are long, the muscles poorly developed and hypotonic. This hypotonicity frequently causes a slight ptosis of the upper eyelids and makes these persons look tired. The diaphragm is low, the heart therefore insufficiently supported and "dropping" or even actually hypoplastic, the abdominal viscera are ptotic, the uterus is often retroverted.

It can scarcely be overemphasized that this asthenic type of *enteroptosis* (*splanchnoptosis, visceroptosis*) represents a constitutional trait and not a disease. The various abdominal complaints of such patients are as a rule due not to the ptosis itself but to the accompanying neuropathic constitution. Too many patients of this type are treated surgically *instead of* psychically. Although such a ptosis may occasionally give rise to a twisting of the ureter or of the renal blood vessels, and although it may predispose to an intestinal volvulus and may cause delayed emptying of the stomach, gallbladder, or renal pelvis, cases requiring surgical treatment for the ptosis are rare exceptions as compared with the large number of neuropathic *asthenics* who are *not* at all or only temporarily

in members of the same family The multiplicity of manifestations of the allergic predisposition is regarded as due to what has been termed 'polypheny," that is, a variety of phenotypic expressions of one gene

> Indeed, the wide range of variation in manifestations has hitherto completely masked the underlying common etiology no one would at first sight recognize allergic reactions in different organs to a wide range of incompatible reagents, covering great variety of clinical form, as a single constitutional entity save for the final evidence of genetic identity [6]

Allergy was found to be 100 per cent concordant in the recorded cases of monozygotic (identical) twins

7 Arthritism

It did not escape the perspicacity of French physicians of the last century that particular diseases such as gout, obesity, diabetes, premature arteriosclerosis, bronchial asthma, migraine, concretions in both the biliary and the urinary tract, tendency to arthritic and neuralgic conditions or to particular dermatoses, are frequently observed in various combinations either in one person or in different members of the same family Arthritism," 'herpetism," or "lithemia" were the terms employed to signify this particular predisposition to the diseases named Although the attempts at a satisfactory explanation of the peculi[illegible] cessful until [illegible] disorders an[illegible] genetics furnished the clue to better understanding, the clinical facts known to the old physicians are occasionally rediscovered by modern authors [7] Their results, however, although obtained with more exact statistical methods, only confirm what has been known for a long time

8 Status Degenerativus

Whatever point of view may be adopted in order to classify various constitutions for medical purposes, it is always some

with dysmenorrhea, the latter indicates nervous hypersensitiveness and hyperirritability, mostly accentuated in and concentrated to the very point by psychogenic factors This old knowledge[2] has been neglected in the last few years Interest was too much preoccupied by the controversy as to whether estrogen, progesterone, androgen, or pituitary sex hormone should be considered the treatment of choice Only recently the psychologic rather than hormonal effect of estrogen upon dysmenorrhea was demonstrated by Boynton and Winther[11]

6 *Diatheses*

The term diathesis has been employed to signify a special tendency to react in an abnormal way to physiologic stimuli and therefore to develop particular diseases We have just mentioned the *fibrous diathesis* and shall discuss the *neoplastic* diathesis later The differentiation of *inflammatory* diathesis of older authors was followed by that of Czerny's *exudative* diathesis, designating a tendency to recurrent inflammations of various mucous membranes and of the skin Increasing knowledge revealed that the manifestations of exudative diathesis are largely allergic in nature As a matter of fact, the use of the term diathesis is not limited to pure constitutional conditions What is called "hemorrhagic" diathesis, for instance, may be an abnormal constitutional state such as that represented in hemophilia or hereditary thrombocytopenia or thrombasthenia, and may be due to vitamin deficiency or to an acquired disease of the hemopoietic system as well

If there is any justification today for the use of the term diathesis it might be with regard to those morbid conditions that are recognized as *allergic* in origin It has been shown, chiefly by Hanhart,[6] that the tendency to allergic states is transmitted as a dominant hereditary characteristic It is not the particular *clinical manifestation that is inherited Nor* does the same substance, protein or other, act as allergen

and clinical medicine justifies differentiation of those individuals who, as a whole, deviate widely from the average, that is, who have to be considered abnormal with regard to numerous constitutional traits

What represents the normal average in a population of living organisms is obviously the best achievable adjustment to the world in which they live Most of the possible variations have already been tried out over and over again and have been rejected as inefficient by the process of natural selection Turned loose, they proved to be poor competitors and were unable to survive Such mutants cannot perpetuate themselves except under favorable conditions of artificial confinement or by what is called domestication This process of domestication in the human race is fostered by advancing culture and civilization In the struggle for life among human beings it is factors other than biologic fitness that are decisive Representatives of constitutional abnormalities, although biologically more poorly adjusted as compared with constitutionally normal persons, are not exposed to a struggle in [illegible]

mutants is virtually guaranteed

Constitutional abnormalities that have lost all importance as selective factors in the maintenance of optimal biologic adaptation of the human race are numerous—refraction anomalies of the eyes, constitutional types of hardness of hearing, contracted pelvis biologic inferiority of the stomach, allergy, diabetes and the like As a matter of fact, constitutional abnormalities are encountered with increasing frequency

In a previous portion of this book we became acquainted with pleiotropism of genes (p 29) Each gene does not only affect a particular part of the body in a particular way, although this particular effect may be the only one visible or otherwise detectable many other parts of the organism may

deviation from the average with regard to particular constitutional traits that is directive Such deviations may pertain to morphologic or functional characteristics or both, or may involve reactions of the body to pathogenic factors What matters, therefore, is the deviation from the average of the population or, we may say, the distinction between normal and abnormal This problem was discussed in chapter 1 It was somewhat arbitrarily assumed that any variation of a constitutional trait occurring in less than 4 5 per cent of all individuals of the population should be called abnormal Variations of a frequency greater than 4 5 per cent should be considered normal The reason for such an assumption is as follows

If we study any constitutional trait that can be expressed by a numerical value, such as height, weight, rate of metabolism, blood pressure, etc, we want to know not only the mean value, but the dispersion about the mean as well The measure of this dispersion is what statisticians call standard deviation or sigma (σ) This is the square root of the sum of the squares of the deviations from the mean, divided by the total number of observations

$$\sigma = \pm\sqrt{\frac{\Sigma pD^2}{n}}$$

where D = deviation from mean value
p = number of individuals showing particular deviation from mean
Σ = sum of squares of all deviations from mean
n = total of all individuals examined

Assuming that we are dealing with chance variation, that is, with binomial distribution of a numerical characteristic, then $\pm 2\sigma$ would include 95 5 per cent of all individuals, and 4 5 per cent would lie beyond $\pm 2\sigma$ This is the reason why we chose this figure as the limit between normal and abnormal This view has been adopted by other students of human constitution [2] Experience gathered from both general biology

the median raphe (cleft arches of one or more vertebrae, fovea coccygea) status dysraphicus is just another name for what had been described and designated as "myelodysplasia" by A Fuchs[10] But what have signs such as crumpling of fingers, especially the little fingers, sternal anomalies, inequality of the mammary glands, or greater span than height, in common with imperfect closure of the neural tube? They are degenerative stigmata that may or may not accompany the latter, but are not in themselves a justification for calling such a condition status dysraphicus

As a matter of fact, neither the number of constitutional abnormalities encountered in a person nor the degree of deviation from the average with regard to each variation is amenable to exact numerical definition, it must be stressed that the limit between normal and abnormal that was previously established is arbitrary too, as must be any similar attempt to classify the fluctuating variety of living organisms What matters here is the fact that individuals whose general constitutions obviously deviate from the average in many respects, are actually biologic liabilities of the race Two instances among many may suffice to illustrate the situation[1]

Many years ago Bumpus studied a large number of sparrows that had been found killed by a tornado They exhibited the most unusual constitutional variations, that is, deviations from the average, with a surprising frequency Extreme variations had therefore proved to be less resistant to the *injurious* action of the tornado

In Sweden light-eyed persons prevail by far over dark-eyed ones Lundborg found the latter to have lower resistance and a greater mortality rate as compared with the average of the population They were encountered more frequently in tuberculosis sanatoria and in institutions for deaf mutes, in houses of correction, and in jails Exactly the opposite was observed in Italy and France, where the light-eyed individuals constitute a minority and were found to be biologically inferior to the

also be involved A gene may extend its activity to several structural characteristics and to functional ones as well, and even to the type of behavior From his extensive studies on the banana fly (Drosophila) T H Morgan[8] writes as follows

> For example, the vitality of the organism is intimately related to some of the most trifling changes in superficial characters, and the productivity and fertility of the animal may be very greatly affected by mutant changes whose visible effects on the body are very slight.

In 1917 these considerations led me to the segregation of individuals exhibiting an accumulation of various constitutional abnormalities Since each such abnormality represents a marked deviation from the average type of the genus and may, at least potentially, involve a diminished adjustment to the environment, the term *status degenerativus* was chosen to signify this state of biologic inferiority, lower resistance, greater morbid predisposition—in brief, the degenerative character of those who manifest it It stands to reason that it is not feasible to fix the number of constitutional abnormalities justifying the diagnosis of status degenerativus It is self evident too that this classification may comprise representatives of all types of abnormal constitution, such as neuropaths, those with endocrine stigmatization, status thymolymphaticus or hypoplasticus, exudative or allergic diathesis, asthenic constitution, or arthritism Status degenerativus is the broadest concept of general constitutional abnormality arising from consideration of general biologic laws

What has been described by Bremer[20] as status dysraphicus, recently studied in this country,[20] is merely a special variety of status degenerativus Status dysraphicus is defined as the result of a faulty closure of the neural tube early in embryonic life and is related quite closely to syringomyelia, as a constitutional substratum for the latter It is readily transmitted to offspring as a dominant charateristic In so far as its symptoms and signs may actually arise from an imperfect closure of the neural tube and a faulty formation of

Representatives of status degenerativus may or may not require medical attention Their constitutional abnormality, however, has to be taken into account so far as the etiology of their ailments, the particular symptomatology of a malady, and its prognosis and treatment are concerned It is not uncommon for a case of status degenerativus to be erroneously taken for one of endocrine abnormality, particularly if unexplained rare pathologic alterations of the central nervous system, of the eyes, ears, or skin are involved Cases of this kind have been reported by Berta Aschner[10] Two more may be briefly reported here from a previous publication[11]

The condition of a married woman about 20 years of age was diagnosed as early Simmonds pituitary cachexia on account of her considerable underweight, the graying of her hair, and a low blood pressure of about 100 systolic. A consideration of the patient s constitution revealed the following facts. She represented the highly nervous asthenic type, with a marked constitutional enteroptosis, and had been underweight all her life The premature graying of her hair was a familial and therefore constitutional trait She noticed her gray hair first at the age of 15, her brother had gray hair at the age of 18, her mother had completely gray hair at 30 years The gray hair in our patient was associated with another abnormality of pigmentation She had large spots of vitiligo chiefly on the chest and back and involving the axillary and pubic hair The symptoms, apparently due to a pituitary insufficiency, were therefore not conclusive at all but *merely signs of a* constitutional abnormality Other symptoms indicating an *anterior* pituitary lobe insufficiency were completely lacking menstruation was *regular* and had been normal since the patient s eleventh year no *abnormalities of* the teeth were present no other signs of premature senescence The *basal* metabolic rate was normal The patient was *extremely nervous* and emotional and suffered occasionally from hysterical *cries*. This neuropathic state accounted also for the dysmenorrhea of which the patient was complaining as the gynecologic examination did *not reveal* any abnormality of the genital organs.

What a difference in prognosis and treatment results in such a case from correct individual analysis and comprehension!

At the twenty third annual *meeting of the* American College of Physicians in New Orleans *in 1939*, I had the opportunity to

better adjusted, average, dark-eyed type Obviously it is not the eye color itself that accounts for such a difference The eye color is merely an indicator of a farther reaching constitutional deviation from the average

It must be borne in mind that biologic inferiority should by no means be confused with social and cultural inferiority Great artists and scientists, leaders in political educational, and other cultural fields are not infrequently constitutional deviants Their specific genius is only one form of constitutional deviation, the frequently accompanying series of others, however, may make them biologic liabilities They frequently have to pay with biologic inferiority for their cultural superiority Beethoven's otosclerosis, Mozart's early tuberculosis Napoleon's familial tendency to cancer of the stomach, are examples Neuropathic constitution, including various socially more or less dangerous psychopathic features, is *not infrequent* in personalities outstanding in one or another cultural aspect[9] I need only refer to some outgrowths of modern art or political systems calling for psychiatric rather than for any *other kind of help*

Recent studies made by the Industrial Health Research Board of the Medical Research Council of Great Britain[10] showed that some individuals in a working group are more liable to accidents than others in the same *circumstances*[11], they may be designated as "prone to accident" It has been found that as few as 10 per cent of a group may be responsible for as many as 75 per cent of the accidents occurring among them *Proneness to accidents may be an innate characteristic* of some people and a personal phenomenon independent of any question of responsibility, conscious action, or blameworthiness Moreover, those who are most often ill tend on the *whole most often to have accidents* Although they are considered to be "fairly normal persons," I venture to assume that a more careful study of these persons would reveal status degenerativus among them with extraordinary frequency

Any constitutional abnormality in an individual may be his only constitutional deviation or may be part of his status degenerativus It can hardly be considered as mere coincidence that patients affected with sickle cell disease were reported to have in addition various constitutional abnormalities other than the sickle cell trait, such as thyreoglossal cyst, congenital cysts and abnormal fissures of the lungs, pseudohermaphroditism, malformations of the heart, hyperplastic thymus, or hereditary deformities of the fingers [1] Just how often the sickle cell trait is only part of a status degenerativus is not known

The accompanying schemes (fig 3) demonstrate three different genetic possibilities accounting for a multiplicity of constitutional deviations in one individual The first scheme illustrates *pleiotropism*, that is, the action of a single gene upon various structures and functions The second represents *linkage of genes* located in the same chromosome and therefore in close relationship with each other as far as the occurrence of mutations and their hereditary transmission is concerned There is no attempt here to enter into a discussion of the consequences of such a linkage of genes and particularly of the principle of crossing over In this respect the reader is referred to textbooks of genetics In a previous chapter (p 29) we met with combinations of various constitutional abnormalities that on the basis of our present knowledge, must be attributed to pleiotropism or to linkage of genes The third scheme shows how in *status degenerativus* different chromosomes are affected without any regularity

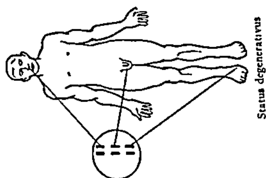
Various combinations of constitutional abnormalities are known to occur in certain families and have been described as special syndromes The association of bizarre skeletal defects and cranial deformities, mental deficiency, corneal cloudiness, and hepatosplenomegaly is known as *Hurler's syndrome*, *gargoylism*, or *dysostosis multiplex* Defects in the mesodermal anlage of the bones are here associated with an "inborn error" of the lipoid metabolism [11] Occurring without feebleminded

present in one of the clinics a 19-year old Negro whose condition had been diagnosed as thyreopituitary insufficiency

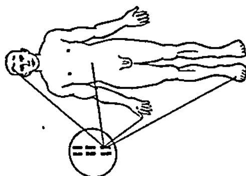
The patient showed stunting of growth, with a retarded bony development corresponding to an age of from 12 to 15 years, was imbecile to a high degree, the root of his nose was sunken, his face was wrinkled as in a far older man, and the thyroid gland was scarcely palpable The basal metabolic rate could not be determined because of lack of cooperation Yet the patient showed symptoms that could not be explained by or were not in accordance with a thyreopituitary insufficiency There was no myxedema, no thickening of the tongue, no umbilical hernia, no constipation, the blood cholesterol was not increased (168 mg per 100 cc.), the genital organs not only were not hypoplastic but were gigantic in size The patient indulged in excessive masturbation and had a strikingly low pitched voice *In addition he presented the typical picture of* a muscular dystrophy of Erb's scapulohumeral type, had disproportionately long arms, was extremely knock kneed had a prognathism, irregularly displaced teeth, and a lymphocytosis of 52 per cent in a total leucocyte count of 7200

This whole complex of signs can be understood only as indicating a combination of various constitutional abnormalities—in other words, status degenerativus To make this term more popular I called the condition "a mess in the chromosomes" when presenting the patient in the clinics

Status degenerativus may or may not comprise abnormal signs that are usually considered indicators of an endocrine abnormality, such as goiter, or disorder of growth, of fat accumulation, of hair distribution, of genital development or function These signs are but coordinated manifestations of status degenerativus They may or may not be caused by a special endocrine disturbance that itself is the consequence of the general constitutional deviation *What must be stressed, however, is the fact that the supposed hormonal disturbance need* not be the cause of other disorders observed in the patient as, for example, those of the nervous system, sensory organs, skin, etc Previously (p 70) we mentioned such an *endocrine stigmatization* as a state of coordination of "endocrine signs" with constitutional abnormalities other than endocrine The importance of a clear conception of such cases is obvious

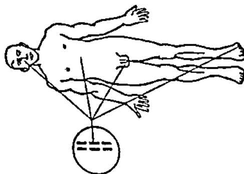


Status degenerativus



Linkage of genes

FIGURE 3



Pleiotropism

ness and clouding of the cornea, the condition is called *Morquio's disease* The combination of webbing of the neck (pterygium colli), cubitus valgus, and infantilism is called *Turner's syndrome*[50] Various other abnormalities may accompany this syndrome There is no justification, however, for attributing this failure of fetal development[51] to ovarian insufficiency[11] or pituitary dysfunction All these syndromes are more or less typical varieties of status degenerativus, each one having its particular familial stamp Some combinations of constitutional abnormalities that include constitutional obesity will be referred to in the following chapter

Multiple cartilaginous exostoses resulting from a disturbance of proliferation and ossification of the bone forming cartilage are known to occur as a hereditary trait,[2] perhaps a mendelian dominant[12] in certain families *Hereditary chondrodysplasia* is the most nearly correct although not officially accepted[12] name for this condition There is a variety of such chondrodysplasia that is associated with multiple hemangiomas and that has been named *Mafucci's syndrome* "it probably belongs to the group of congenital mesodermic dysplasias"[53] Multiple angiomas, however, may be found also in combination with other constitutional anomalies, for instance with Recklinghausen's neurofibromatosis In this connection it may be well to recall *Albright's syndrome*, which has been discussed in a previous chapter

The endocrine system is directly involved in the peculiar state described as *Werner's syndrome* by Oppenheimer and Kugel[12 55] It may be defined as a rare heredofamilial disorder comprising scleropoikiloderma, bilateral juvenile cataract, premature graying and loss of hair, laryngeal changes, endocrine stigmatization of a pluriglandular type (atrophy of the testes, adenomas of the thyroid and adrenals, and "evidence of hyper activity of the parathyroid"), and constitutional inferiority Osteoporosis and calcification of the soft tissues, particularly of the blood vessels, are prominent

having been exposed to roentgen irradiation This theory assumes that all abnormalities encountered in these syndromes are caused by the damaging effects of blebs containing cerebrospinal fluid that has escaped from the medullary tube into the subcutaneous tissue through a gap in the roof of the developing fourth ventricle (foramen anterius) in early embryonic life The tendency to such abnormal bleb formation is held to be caused by one main recessive gene Other modifying genes are considered responsible for the localization of the blebs and thereby for the great variety of deformities and syndromes One can hardly believe that this theory offers a satisfactory explanation of the facts Too frequently we meet with single hereditary abnormalities occurring through generations of a family, such as cutis laxa, weblike folds between the fingers, pterygium colli, oxycephaly, Sprengel's deformity of the shoulder blade, hypertelorism (wide distance between the eyes), high (arched) palate, contractures of interphalangeal joints, and many others They represent what are known as *degenerative stigmata* and can hardly be accounted for by bleb formations occurring regularly at the same spot in the embryonic body

Not uncommon degenerative stigmata are irregularities of dentition and the fissured, fleshy, and deeply red tongue known as lingua plicata or lingua scrotalis[2] It is frequently an accompaniment of neuropathic constitution and a hereditary trait It should not be confused with avitaminosis or with lingua geographica, as is done by A Werner,[40] who publishes a picture of such a lingua plicata in mongolism and calls it lingua geographica Some of these degenerative stigmata represent partial infantilisms, or more correctly fetalisms, that is, the abnormal arrest and persistence of infantile or fetal developmental states This is true for hyperextensibility of the finger joints, for hypertelorism, and for other states

As a matter of fact, accumulation of degenerative stigmata is frequently encountered in persons affected with diseases

Hyperelasticity and hyperlaxity of the skin, known as cutis laxa, have been observed as part of a syndrome comprising besides cutis laxa, cutaneous fragility, that is, ready susceptibility to bruising, and articular hyperlaxity[35, 36] This syndrome has also been called *Ehlers' syndrome* More frequently its parts occur dissociated as single degenerative stigmata Hyperextensibility of metacarpophalangeal and interphalangeal joints as well as of elbows may, because of its very frequent occurrence in Negroes, not be considered as a degenerative stigma in this race Hypermobility of the joints due to relaxation of the ligaments is also a frequent attribute of the syndrome consisting of blue sclerotics, brittle bones, and deafness[15] that has previously been discussed Readiness of the skin to bruise owing to fragility of the cutaneous blood vessels has long been known as a degenerative stigma[2]

Cutis laxa and particularly redundancy of the skin folds of the neck are a frequent though by no means pathognomonic sign of mongoloid idiocy[37] It occurs as well in endemic cretinism, as contrasted with infantile or adult myxedema[2] In one family it was found as a hereditary trait persisting for 300 years[38] *Mongolism* is quite a collection of degenerative signs "certainly the more one studies these persons, the less one is able to find anything normal about them" (Bleyer)[37] Hence it is not surprising to find abnormalities of endocrine glands[39] as well as developmental defects of the brain[2] in mongoloid imbecility and idiocy It is not surprising either that the abnormalities observed in the pituitary are not uniform and seem confusing All that is surprising is the conclusion[39] proffered that an endocrine disorder of the pituitary body accounts for the various developmental disorders of mongolism after birth

A strange theory has recently been advanced for the morphogenesis of gargoylism and the previously named related syndromes[33] It is based on embryogenetic studies carried out on mice that exhibited various inheritable malformations after

construction of a peptic ulcer type, a gallbladder type, or a pernicious anemia type of habitus Even fine details such as hand and nail shapes or the tooth pattern were included in the characteristics of such types Psychologic features were added later to complete the picture of personality types with certain morbid predispositions[53]

From our previous discussion, and particularly from the knowledge of both pleiotropism and linkage of genes, we see that such relationships between habitus, psychologic characteristics, and morbid predisposition may exist There can be little doubt that there is a great deal of truth in Kretschmer's concept Slender, asthenic individuals are likely to be of *schizoid* temperament, whereas broad, pyknic persons more frequently represent *cycloid* or *cyclothymic* personalities The etiology and pathogenesis of most disease, however, is too complicated to conform to so simple a concept as that mentioned One can hardly expect to find an ulcer or gallbladder type of human habitus What may be and actually has been found, however, is a greater frequency of various diseases in persons exhibiting a particular habitus

Stockard[11] is quite right in stating that "undoubtedly much time and effort have been fruitlessly spent in making many careful measurements of meaningless characters" New results of importance are, in my opinion, not to be expected from a further complication and refinement of anthropologic measurements*, nor are they to be expected from a new ter-

* In this respect it is interesting to mention [illegible] of a daily newspaper under t[illegible] The story goes as follows " [illegible] so on, local scientists will te[illegible] you [illegible] you are capable of comm[illegible] a [illegible] the test depends on the finding that a great number of inherited *physical characteristics* are linked inseparably from birth to certain powerful mental, moral and even artistic tendencies " This seems to be a utopian outgrowth of an originally sound concept.

arising from abnormal constitutional background In relation to rheumatic fever, for instance, it has recently again been emphasized by Draper et al,[63] who thereby confirm the findings of previous authors[2]

Status degenerativus is in our opinion a multiple genopathy a more or less generalized alteration of the chromosomal pattern as compared with the average pattern The latter, however, is for obvious reasons better equipped and better adjusted to the environment Status degenerativus comprises the whole gamut of disorders starting with the multiple malformations that preclude extra-uterine life and ending with the deviations of individuals who do not require any medical attention at all for their constitutional abnormalities They may, however, be known as queer persons and cranks, may be predisposed to various diseases arising from abnormal constitutional background, or may show unusual clinical features and unusual response to therapeutic procedures and be poor medical and surgical risks in general

9 Habitus Classification and Relation to Other Constitutional Traits and to Morbid Predisposition

Attempts to classify individual constitutions that lie within the limits of normality are based on studies of the general make up or of what is known as the *habitus* of a person The results of these studies are not in proportion to the painstaking work spent on this purpose Many physicians believe that the essential if not the only objective of constitutional pathology is the detection of relationships between the individual habitus the proportions and measurements of the body, on the one hand, and the reactions of the individual to various stimuli, and particularly certain disease inclinations, on the other They believe that constitutional pathology must find out as many details of the general make up as possible that may correlate with a particular morbid predisposition

The culmination of these attempts is George Draper's[3]

developed muscular system What Kretschmer called the *dysplastic* type includes individuals in whom status degeneratıvus is visible from the habitus because of various irregular deviations from the usual body measurements and proportions

As far as typing of female individuals is concerned the distribution of *subcutaneous adipose tissue* over various parts of the body surface represents a striking constitutional characteristic[1,3] In the majority of women the subcutaneous adipose tissue is accumulated chiefly around the hips and on the thighs the lower part of the abdomen the buttocks, and the back, as illustrated by Rubens favorite subjects One may therefore call this variety the Rubens type It corresponds to what is known as the *girdle* type of fat distribution Other women show a particular accumulation of fat tissue in the trochanteric region protruding from the outline of the body One may call this variety the *breeches* or *trochanteric* type of fat distribution Some women are annoyed by more or less marked accumulation of fat in the lower extremities, usually extending from the hips to the knees or the ankles In some women the excess fat tissue is limited to the calves or ankles In more pronounced cases of this *inferior* type of fat distribution, the fatty masses are arranged like clusters and the skin on the surface of the thighs is consequently covered with dimples The opposite or *superior* type of fat distribution is seen in women with relatively slender legs and abdomen and rather marked accumulation of fat in the back, the upper parts of the arms, the breasts the neck, and the face Sometimes the unusual accumulation is limited to the breasts or the buttocks The latter state called *steatopygia*, is a racial characteristic of certain Negro tribes As a matter of fact there are also borderline conditions and combinations of these pure types

As has been pointed out elsewhere,[3] these varieties of distribution of the subcutaneous adipose tissue are constitutional in nature and not due to endocrine dysfunctions State

minology In fact there are two types of deviation from the average as far as habitus is concerned They have been recognized since ancient times and the change of names has added little to the facts About 2500 years ago, Hippocrates distinguished a long, thin and a short, thick type of human being The first designation applies to the slender, longitudinal, though not necessarily tall individuals, the second to the broad and stocky persons whose features and organs, as Stockard puts it, are "spread and voluminous instead of linear"

The need for particular terms to signify these two types of human beings arose from various concepts about their nature or from observed relationships of these types to special functional features and groups of diseases

The longitudinal type has been denoted as follows· habitus longilineus, or slender, linear, leptosome, stenoplastic, hypotonic, microsplanchnic, hypovegetative, hyperontomorphic, ectomorphic, asthenic, phthisic type

The lateral type has been labeled as habitus brevilineus or *quadratus, or eurysome, euryplastic, hypertonic,* megalosplanchnic, hypervegetative, hypo ontomorphic, endomorphic, hypersthenic, pyknic, plethoric, arthritic, apoplectic type

There are, of course, no sharp borderlines between these two types and the intermediate average, which may be termed *normotype*, and which has also been called mesoplastic, normo splanchnic, meso ontomorphic, or mesomorphic

Occasionally some more specific classifications have been attempted, which, however, do not differ greatly from the three essential groups just mentioned Sigaud, for instance, distinguished four types of human beings *typus respiratorius, cerebralis, muscularis*, and *digestivus* The first two are only varieties of the longitudinal type The digestive type corresponds to the lateral Kretschmer's *athletic* type corresponds to Sigaud's muscular type, and both are varieties of the intermediate normotype, distinguished by a particularly well

developed muscular system What Kretschmer called the *dysplastic* type includes individuals in whom status degenerativus is visible from the habitus because of various irregular deviations from the usual body measurements and proportions

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ments to the contrary are erroneous and do not gain weight by being transmitted from one textbook or paper to generations of subsequent ones

A great variety of *somatic indices* have been devised, as calculated from various measurements [2] In so far as they are employed by themselves to represent constitutional types, they cannot be anything but disappointing Yet they are more or less valuable for statistical studies concerned with individual body build Hence anthropology is more interested in them than is applied constitutional pathology An excellent review of this subject has been given by Tucker and Lessa [15]

It must be stressed again that habitus is not to be confused with constitution It is, in its various components, determined chiefly by genes, but is also modifiable in part by environmental factors such as nutrition, sunlight, and physical exercise Moreover, habitus is not necessarily fixed throughout life, as some authorities[14] believe With increasing age the chest assumes more or less the characteristics of the lateral type The ribs and the diaphragm become more elevated, the epigastric angle more obtuse, and abdominal fat accumulation increases [2] Hence Sigaud's digestive type, which is virtually the lateral type has been found to be more frequent among men of more advanced age than among those in the third decade (H Zweig) [2]

Signs and features described as characteristic of the longitudinal and the lateral type respectively are as a matter of fact, quite frequently the product of human imagination and the tendency to schematization Most authors, for example, consider the longitudinal, asthenic type to be longheaded (dolichocephalic), whereas the lateral type is shortheaded (brachycephalic) Kretschmer, however, found more frequently among his asthenics a short head of medium width [2] A narrow and highly arched palate is not encountered exclusively in longitudinal types [2] Stockard describes the longitudinal type as usually farsighted and the lateral type as nearsighted Exactly the opposite result was obtained by

Pryor[15] in her studies on the relationship of eyes to body build Stockard's further statement that persons of the longitudinal type arrive at puberty early rather than late, and that the male develops a large, strong larynx and a low pitched bass or baritone voice, whereas the lateral type arrives at puberty a little later than the linear, and the voice is high pitched (tenor in men), cannot be accepted as a general rule Good reviews of the history, technic, and results of somatotyping have been given by Tucker and Lessa[16] and by W H Sheldon[17] It may therefore be sufficient to describe the outstanding characteristics of the two main types of human habitus quite briefly

In the longitudinal type the trunk is narrow, tapering to the waist, the epigastric angle is acute, the chest is long as compared with the abdomen, the neck is long and small in circumference, the extremities are long and slender, with long slender muscles and slender bones There is scanty accumulation of adipose tissue If the shape of the head accords with the general trend of the habitus—as is not always the case—the head is dolichocephalic, the face leptoprosopic—that is, its longitudinal measurements exceed the lateral to a greater degree than in the normotype The interpupillary distance *is short*, the eyes are close together, the nose bridge is narrow, the lower jaw small and narrow

The lateral type represents the antithesis of the longitudinal type in all the respects mentioned The trunk is wide, the epigastric angle obtuse, the chest short as compared with the abdomen the neck short and wide, the extremities relatively short and stocky, with thick bones There is a tendency to accumulate relatively more adipose tissue as compared with the normotype The head is usually brachycephalic, the face euryprosopic, that is, its lateral measurements are excessive as compared with the normotype or longitudinal type The interpupillary *distance is* great, the eyes are far apart, the nose bridge is wide, the lower jaw is large

As a matter of fact the relative size, shape, and *position of*

the viscera are intimately correlated with the general make up In other words, a characteristic internal habitus, if we may use such a term, corresponds to the external one It was first shown by Beneke[2] that in the longitudinal type the heart is relatively small, the arterial blood vessels narrow, the lungs large, the liver small, and the small intestines short, whereas the lateral type is possessed of a relatively large heart, wide arteries, short, small lungs, large liver, and long intestines Of greater clinical importance is the knowledge that it is the longitudinal type in which fluoroscopic examination reveals a dropping heart, or at least a longitudinal heart shadow, and a long, narrow, vertical stomach extending far down in the abdomen Contrariwise, we encounter a more transverse position of the heart, an elevated diaphragm, and an oblique situation of the stomach in the lateral type The differences in the electrocardiograms of the two types resulting from the difference in position of the heart are self evident

We see and understand from our discussion above that there are certain relationships between the general make up of a person and some functional characteristics, both physical and mental

Blood pressure, both systolic and diastolic, is on an average somewhat higher in the lateral than in the longitudinal type [17,18] Differences between the longitudinal and the lateral type have been found with regard to the functional behavior of the hemopoietic and the vasomotor system, the capillary permeability, respiration, and various metabolic functions [15,17,19] Such differences, however, exist only in relation to the average, that is, they are significant statistically, not individually As far as a correlation between somatic type and mental attitude is concerned, no further discoveries have resulted since Kretschmer's time from extensive studies carried out along these lines by various authors Longitudinal types are preferentially of schizoid temperament or introvert, lateral types are more frequently of cycloid temperament or extrovert Hence the

first group is more inclined to develop schizophrenic, the latter manic-depressive types of psychosis, if any Attempts to correlate the habitus with certain mental characteristics such as intelligence, sociability, perseverance, leadership, aggressiveness, and emotional excitability[17] did not reveal anything beyond Kretschmer's concept

There is no question that a relationship between habitus and constitutional predisposition to certain diseases does exist This is expressed by the old terms habitus phthisicus, apoplecticus arthriticus It is owing to a misunderstanding of the underlying biologic principles, however, when Feigenbaum and Howat[29] complain of the "erroneous perpetuation of a clinical impression namely, that the *anatomic* habitus is one of the causes of disease" The anatomic habitus is *merely* the visible, external expression of certain genes simultaneously influencing internal structures and various reactions of the organism and creating thereby certain morbid predispositions Habitus is never the cause of a disease, although habitus and constitutional predisposition to certain diseases may have a common root in particular genes Therefore habitus may be an indicator of such a morbid predisposition

In 1918 the relation between habitus and morbidity was studied in 2000 male patients observed in Vienna[2] The greater tendency to pulmonary tuberculosis in the longitudinal type was confirmed The muscular and digestive (lateral) type of person had a greater tendency to develop syphilitic aortitis and nephritis the muscular type had greater disposition to neuralgic, myalgic or arthralgic pain Individuals of muscular habitus were more frequently affected with catarrhal conditions of the upper respiratory tract and with nervous disorders of the heart Cerebral types presented neurotic conditions with particular frequency as compared with persons of other types

Stiller was one of the first to note the great frequency of the asthenic habitus in patients with peptic ulcer Quite a litera

ture developed on this subject. The culmination of these studies was G Draper's[8] delineation of an "ulcer race" as *contrasted with* a "gallbladder race." Practically, the first corresponds to the longitudinal, the latter to the lateral habitus[14] Even if a definite relation between these two diseases and the habitus of their *victims were* established beyond doubt, we would not be justified in designating the habitus according to one of the various diseases to which the possessors of this habitus are predisposed This is all the more true if such a relationship is not proved beyond any doubt Tucker and Lessa[18] report some of the controversial literature Our own studies of 132 ulcer patients in Vienna showed that a somewhat greater frequency of the longitudinal *habitus in* ulcer patients as compared with the average population is not statistically significant[2,21] In other words, a definite relationship between *peptic* ulcer and habitus does not exist, at least not in the population of Vienna It may be different in Chicago, according to recent investigations[22] It may also be true that persons of the longitudinal type, with long, vertically situated stomach, are more likely to develop ulcer at the lesser curvature, whereas those of more lateral habitus, with the stomach in oblique position, more frequently develop ulcer in the pyloric region and in the duodenum[2,15]

The relationship between constitutional predisposition to gallstones and lateral habitus was well known to older generations of physicians Gallstones were considered one of the foremost manifestations of "arthritism," and "arthritic habitus" is identical with the lateral type Yet I believe that Stiller was right in emphasizing that young individuals, particularly young men, who suffer from gallstones are chiefly of the asthenic type[2] And what about the not altogether uncommon occurrence of ulcer plus gallbladder disease in the same *individual?* There can be only a superficial, indirect relationship between these diseases and the somatic type of a person Such a relationship, although statistically significant, is not valid in the individual case

Recently Robinson and Brucer[18] tried again to establish a relationship between body build and arterial hypertension They found that individuals of lateral type have as a rule a somewhat higher systolic and diastolic pressure than those of longitudinal build and show a higher incidence of arterial hypertension This was found to be true particularly of tall persons of lateral habitus The work of these authors was severely criticized with regard to biased applications of statistical methods[21] In my opinion it is paramount to take into account the fact that maintenance and regulation of blood pressure at a somewhat higher than average level is not necessarily an indicator of future essential hypertension According to my own experience essential hypertension may be encountered in both lateral and longitudinal types The same holds true for essential constitutional hypotension

A relationship between body build and chronic arthritis was found by Kovacs and Hartung[15] They confirmed the impression of earlier observers that rheumatoid arthritis is more often associated with a longitudinal osteo arthritis with a lateral habitus[41] Persons with prostatic hypertrophy are known to be more usually of the lateral type[4, 33] Details of their habitus were studied by Blatt[6] and later by Draper et al[14]

A modern German otologist M Schwarz[24] goes so far as to contend that body build may be of diagnostic value in differentiating otosclerosis from chronic adhesive processes of the middle ear Patients with otosclerosis are supposed to be of the asthenic type whereas those with adhesive otitis more frequently represent the lateral and muscular habitus This assertion is misleading It was pointed out as early as 1914 that no relationship exists between otosclerosis and particular habitus[25]

The two types described above actually occur among all races and nations It stands to reason however, that the relative frequencies of the somatic types are different in various populations and races In this connection it is interesting that

according to Stockard "the British may be called a linear type race, and the Germans a lateral type race." This, as a matter of fact, is true only so far as the majority of the populations of these nations respectively is concerned.

It has been pointed out that the anatomic habitus must never be considered one of the causes of a disease. Habitus and constitutional predisposition to certain diseases may, however, be common results of particular genes whose sphere of action extends far beyond a single special morphologic or functional trait. Besides the visible or otherwise readily detectable phenotypical effects of a gene or gene complex, there may be various side effects pertaining to a special morbid predisposition. The same basic principle accounts for a great part of what is known as *sex incidence* of diseases. It is these side effects of the genetic sex anlage that may be responsible for the prevalence of certain diseases in one or the other sex. An apparently quite similar concept has been expressed by Draper et al.[25]

We are not considering such diseases as hemophilia or color blindness, the sex incidence of which results from linkage of the pathologic gene with the sex gene, that is, from the localization of both genes in the sex chromosome. We are thinking of various diseases with exclusively or partially constitutional etiology that befall one sex or the other by preference. It is erroneous in this connection to consider the gonadal hormones instead of the sex chromosomes and to derive a hormonal therapy from such a concept. The presence of two x chromosomes in an individual does far more than to induce the development of ovaries supplying the body with ovarian hormone. Attempts to cure or prevent hemophilia, retinitis pigmentosa, thrombo angiitis obliterans,[26] or peptic ulcer[27] by means of estrogenic hormone must eventually prove futile.[28] Some beneficial results, however, may be obtained through the unspecific pharmacodynamic action, particularly the vasodilating effect of estrogenic hormone.

VII

SOME MAJOR DISEASES WITH CHIEFLY CONSTITUTIONAL ETIOLOGY

THAT heredity is a more or less important factor in the etiology of various diseases is practically all that medical textbooks say about constitutional background In the following discussion, an attempt is made to demonstrate how a clearer concept may be obtained as to the manner in which heredity operates Some major diseases are considered here in order to illustrate the principles emerging from the facts that have been discussed in the foregoing parts of this book

1 METABOLIC DISEASES

There are "inborn errors of metabolism," to use Sir Archibald Garrod's expression, that represent relatively simple situations Alkaptonuria, cystinuria, constitutional porphyrinuria, pentosuria, and fructosuria are due to abnormal genes acting upon a particular chemical reaction in the body Certain products in the intermediary metabolism are not broken down, presumably because of lack of the appropriate enzymes It seems justifiable to assume that alkaptonuria behaves as a recessive mendelian characteristic The mode of hereditary transmission of the other metabolic disorders named seems to vary in different families [1,2,3]

A far more complicated situation exists in the case of those "inborn errors of metabolism" that are due to abnormal genes

acting upon several organs involved in one particular bodily function, and not upon a single chemical reaction. Such functions are the regulation of carbohydrate metabolism, in particular the maintenance of a normal blood sugar level, and the regulation of fat deposit throughout the body, with attainment and maintenance of a certain amount of accumulated adipose tissue. Derangement of the first function causes diabetes mellitus; of the second, obesity.

a) DIABETES MELLITUS

There is unanimity regarding the etiology of diabetes. The essential etiologic factor in this disease is a hereditary, constitutional anlage. Except for the relatively few cases of what we may call symptomatic diabetes, accompanying inflammatory or neoplastic processes of the pancreas, suprarenals, or pituitary, heredity is the most frequently encountered causal factor. Environmental influences such as previous infections, intoxications, dietetic indiscretions, or emotional upsets may at best cooperate in advancing the manifestation of the preexistent anlage. Attempts to elucidate the mode of hereditary transmission of this anlage have failed, and more recent investigations of this subject have not added anything essential to what has long been known. Presumably this is due to the fact that more than one abnormal gene is involved and that dominance or recessiveness is not an invariable attribute of a gene.

As far as the pathogenesis is concerned, it has always been my belief[1] that diabetes mellitus cannot be considered a disease merely of the Langerhans islets of the pancreas Other endocrine glands such as the pituitary and adrenals, and indirectly the thyroid, parathyroids, and gonads, are involved in the regulatory mechanism of carbohydrate metabolism. The autonomic nervous system and, last but not least, the liver are of equal importance in this respect. The nervous system not only regulates the function of the endocrine glands and the proper liberation of the respective hormones at the proper time,

but takes a direct part in regulating hepatic glycogenolysis Attempts have been made to distinguish between the different varieties of diabetes Obese and lean, hypersthenic and asthenic, insulin sensitive and insulin resistant types have been distinguished On the basis of our more profound knowledge of the pertinent facts, Soskin[4] reaches the following conclusion

It is thus possible, in view of the fact that pancreatic pathology is not usually found in diabetes mellitus, that this syndrome may include cases of pancreatic and of pituitary diabetes and, less probably, thyroid and adrenal cortical diabetes. It is even more likely that certain cases may be termed hepatic diabetes, when the damaged liver fails to respond normally to the presence of a normal amount of insulin

It should be noted that Soskin is speaking of diabetes mellitus as a syndrome, not as a disease Although we do not yet possess suitable methods of differentiating clinically the above named varieties of diabetes,[8] and dogmatic classification into a pancreatic and a pituitary type[74] seems to be somewhat premature, the basic idea is sound, in so far as the various links in the metabolic chain may have a different share in the pathogenesis of diabetes It can hardly be denied, however, that diabetes mellitus in its different varieties represents one entity, a true disease, caused by the same pathologic gene complex This gene complex extends its activity not only to a single chemical reaction, or to the structure and function of one particular organ, such as the pancreatic islets, its sphere of action includes all structures and functions participating in the regulation of carbohydrate metabolism and in the maintenance of a normal blood sugar level[8]

Mitchell and Angrist[44] studied 18 cases in which small areas of focal necrosis of the adrenal cortex were found at autopsy Although this finding has no clinical application at present, it does not seem to be a pure chance coincidence that 5 of these 18 cases were those of diabetics, one of them presenting Cushing's syndrome with obesity, hirsutism, hypertension, and a basophilic adenoma of the pituitary The areas of focal

necrosis in the adrenal cortex do certainly not account for the diabetes, they are, however, suggestive of involvement of the adrenal glands in the sphere of action of the diabetic anlage. They indicate a "weak spot" in persons who have diabetes. As a matter of fact, this condition is something quite different from a "symptomatic diabetes" that arises from a tumor of the adrenal cortex[55] or from a pheochromocytoma of the adrenal medulla,[84] and that is cured by surgical removal of the tumor. The clinical pictures of the constitutional and of the symptomatic variety of diabetes may be the same.

There are strains of mice exhibiting hyperglycemia and alimentary glycosuria. Abnormal changes in the pancreatic structure could not be detected in these mice.[7] Adrenal medullectomy, however, corrected the abnormal glucose tolerance curve.[64] It was found that spontaneous hyperglycemia as well as spontaneous hypoglycemia occurring in certain mouse strains were both recessive to normal blood sugar levels, and apparently belong to the same allelic series, with high blood sugar dominant over low.[8]

The "renal threshold" of blood sugar does not seem to be included in the sphere of action of the genes producing diabetes mellitus. Although families have been reported in which some members had renal glycosuria and others suffered from severe diabetes mellitus,[75] it was shown by Joslin and his co-workers[9] that none of 67 cases satisfying the criteria for renal glycosuria later developed diabetes mellitus.[10] Diabetes mellitus has also been reported as occurring in families affected with various "metabolic errors" such as pentosuria, fructosuria, and cystinuria.[1]

b) OBESITY

We meet with an even more intricate situation in obesity. Again we can distinguish a symptomatic and a constitutional variety. In the first, obesity develops as the result of a tumor or other pathologic process in one of the endocrine glands or

is caused by a cerebral lesion Hence it is justifiable to speak of a hypothyroid, a hypogonadal, an adrenal, a pituitary, and a cerebral type of obesity The symptomatic variety is infrequent Among 275 unselected cases of high grade obesity, there were only 5 cases of endocrine and 2 cases of cerebral adiposity In all of the remaining 268 cases no such diagnosis could be made If some symptoms or signs suggestive of an endocrine disturbance were found, they were evidence not that an endocrine disease was causing the obesity, but merely of what we call endocrine stigmatization These 268 cases represented the far more frequent constitutional variety of obesity

It may be surprising that we have omitted completely the so-called exogenous type of obesity, although this is considered by many authorities to be the most frequent one Frankly, I do not believe that pure exogenous obesity exists at all What can be produced by artificial overfeeding or artificial restriction of muscular exercise is overweight or corpulence of temporary character, not obesity Obesity should be defined as the compulsory tendency to marked overweight due to abnormal accumulation of fat in persons who are left to their automatic regulations, and who are not supervised so far as intake of food and expenditure of energy are concerned All obese persons must have a certain individual predisposition, that is, they must have a weight regulating mechanism that is more readily overthrown than a normal one All cases of obesity are to a variable extent endogenous and constitutional in origin It has been pointed out elsewhere[11] in more detail that an increased appetite, with a subsequent imbalance between intake and output of energy, is the consequence of an abnormal anlage rather than the cause of obesity Obesity is a definite metabolic disease, while corpulence of temporary character is *not*

An experimental confirmation of our view was recently furnished by Hetherington and Ranson[14] Rats with hypothalamic lesions that frequently cause obesity tend to indulge in

much less spontaneous running than do the majority of normal controls, or than was exhibited preoperatively. In addition, the food consumption of the obese rats may greatly exceed the intake of the normal litter mate controls Yet it was found that animals that have somewhat similar lesions of the hypothalamus, but that do not grow obese, also indulge in much less spontaneous activity, though perhaps not in as little as fat rats On the other hand, rats may grow fat even when food intake is limited to an amount equal to or even a little smaller than that allowed normal litter mates The idea is suggested by the authors "that the obese animal's efforts to increase food intake and cut down energy expenditure are indicative of a partial inability on the part of its physiological mechanism to metabolize easily all of its available food stores"

A similar situation is encountered in young normal rats when treated with growth-promoting hormone from the anterior pituitary gland These rats gain significantly more weight than do untreated litter mates, although food intakes are kept identical for experimental and control animals This fact, observed by Lee and Schaffer[67] and by the H M Evans group of investigators,[67] led to the conclusion that the growth promoting action of the hormone cannot be ascribed to increased food intake The resulting deposit of tissue substance must therefore be considered a consequence of better utilization of the food eaten

Obesity is a true metabolic disease bearing upon the intermediary metabolism

There can hardly be any further discussion about the hereditary character of obesity Those who are still in doubt in this respect may change their minds in view of the following facts.

(1) In an analysis of 275 unselected cases of obesity, it was found that in 73 per cent of them one or both of the patient's parents were obese If members of the family other than the parents were included, a hereditary factor was suggested in 88 per cent of the cases These figures can be approximately

confirmed in a collection of material of at least 1000 cases The figures are significant even with full consideration of the great frequency of obesity They were obtained in Vienna and correspond to those found in Chicago by Rony[11] In Rony s series of 250 unselected cases of obesity, 69 per cent of the patients had at least one obese parent

As a matter of fact, the constitutional character of a particular case of obesity cannot be ruled out even though no other members of the patient's family can be found who are obese This results from the laws of heredity The fact must be stressed that in families affected with the hereditary trait of obesity, the condition is not exhibited by all members of the family If, in spite of similar educational influence and similar environment, obesity develops in *some members* of a family and not in others, this finding is in full accordance with the laws of heredity It does not, however, support the theory that particular habits arising from environment and education may account for an imbalance between food intake and energy output

(2) Observations on identical twins with regard to body weight have been discussed in chapter I They demonstrate conclusively the dependence of body weight on genetic factors This conclusion is particularly dependent on studies of obese twins[12]

(3) It fits into the general panel of the physiology of genes that the time of actual manifestation of their potentialities may vary in different strains As far as the genes accounting for obesity are concerned, their manifestation in exceptional cases may take place soon after birth or even in fetal life These are the cases described by T Christiansen as "macrosomia adiposa congenita"[13] In the family reported by this author, two sisters had five children each Three and four respectively of the two sets of children were rather large at birth These babies immediately after birth displayed extraordinary appetites, grew very rapidly, and accumulated prodigious

amounts of fat Only one of them survived the first year Autopsy performed in 1 case did not reveal any explanation of the peculiar condition From this observation the inference must likewise be drawn that overfeeding must be considered the compulsory consequence rather than the cause of obesity Overfeeding is nothing but the indispensable means to the realization of the potentialities of the abnormal anlage Two more cases of macrosomia adiposa congenita were reported elsewhere [13]

(4) C H Danforth bred a strain of yellow mice presenting extreme obesity as a hereditary, dominant mendelian characteristic Neither macroscopic nor microscopic examination revealed any abnormality to explain it It is particularly interesting, in relation to Christiansen's observation, that in Danforth's strain of mice the pathologic anlage to obesity proved to be a so-called lethal factor when it was inherited from both parents, that is, when the mouse was a homozygote in respect to the abnormal character

To deny the role of heredity in obesity is impossible if the aforementioned facts are not ignored

Since the genetic origin of obesity is an established fact, attempts have been made to discover the genetic laws that govern the transmission of the hereditary tendency to obesity In the strain of obese mice studied by Danforth, a single dominant factor was found to account for the abnormal condition This factor apparently also produced the yellow coloring of the affected animals This probably is indicative of a pleiotropic action of the pathologic gene Obesity in humans was attributed to multiple dominant factors The number of these factors was assumed to vary in different families from one to four or more [12] In any case it is agreed that stoutness is partially dominant over leanness This is in accordance with the occasional occurrence of strikingly lean persons in families exhibiting the obesity trait in most of their members

The genetic factor accounting for the various female types

of distribution of subcutaneous adipose tissue is sex limited, that is, this factor is active only in females It can, however, be carried by males and be transmitted to their daughters This is particularly evident in relation to steatopygia, which is a racial characteristic of Bushman and Hottentot women It does not occur in the male Such a sex limited heredity is of course entirely different from sex linked heredity In the latter the particular gene is carried in the x-chromosome and its manifestation does not preclude the male sex On the contrary, if the sex linked characteristic is recessive, it becomes manifest almost exclusively in the male Therefore a mistake inheres in Rony's view[11] that steatopygia is "undoubtedly an hereditary, sex linked characteristic"

The problem of paramount interest is the pathogenesis of obesity, since its etiology has been recognized in abnormal hereditary factors In other words, how does heredity bring about obesity? Which anatomic structures or which functions are influenced by the abnormal gene or gene complex accounting for obesity?

In order to have a clear idea of the problem some misconceptions must first be corrected Rony,[11] for instance, puts the question as follows "Which tissue or organ anlage carries the genetic factors that make for the fat content of the body?" As all genetic factors are present in the fertilized ovum and are, by virtue of mitotic cell division, transmitted to each cell derived from the fertilized ovum, the question must be put differently In which tissue and in which functions of the organism are the genetic factors operative that make for the fat content of the body? To make it clear The hereditary factor accounting for hair color is operative only in the structures involved in the development of hair, the hereditary factors accounting for particular psychic endowments, such as musical or mathematical talent, are active in certain cell groups of the brain only All genes, however, were present in the fertilized ovum and carried in all cells that were derived from

this ovum by mitotic cell division The progressive differentiation and specialization of various cell groups is directed by certain genes whose potential energies are being discharged and gradually exhausted *The prospective germ cells are the only* ones that preserve the sum total of the potential energies that were transmitted to them from the fertilized ovum This preservation means life, exhaustion means death

We meet with another misconception in a review published by Ryne\arson and Hildebrand[14] *in which they make the following* statement

> Briefly, obesity is attributed to one of the following conditions (*a*) disturbance in the nervous system including both the cerebrospinal and the autonomic division (*b*) disturbance in the intermediary metabolism of both *fat and carbohydrate* (*c*) *an inherited abnormal anlage for obesity (Bauer)* or (*d*) variation in the tendency of the adipose tissue to accumulate fat (lipophilia) In this last hypothesis it is assumed that the adipose tissue *of the obese person differs from that of the normal person in that it has a* greater tendency to accumulate fat and a greater resistance to the mobilization of fat The majority of authors concluded that none of these theories *may be applied to all or even to a large percentage of obese patients*

This is a misconception, in so far as conditions *a*, *b*, and *d* concern the pathogenesis, whereas condition *c* concerns the etiology of obesity Furthermore, conditions *a*, *b*, and *d* are not alternatives but are related to one another in so far as each may involve the others

Logical interpretation of facts leads to a different concept [11] *The gene or gene complex causing obesity exerts its* influence upon (*a*) the local lipophilia of the adipose tissue, (*b*) some of the endocrine glands, and (*c*) those parts of the central nervous system that regulate lipophilia and dominate metabolic functions, as well as those that are the site of the general feelings ruling intake of food and expenditure of energy This is assumed for the following reasons

(1) The unequal distribution of subcutaneous adipose tissue is the expression *of regional differences in* "*lipophilia*, that is,

of the tendency to deposit fat, as well as of resistance to its mobilization The different varieties of fat distribution and regional accumulation of adipose tissue in women (p 161) represent hereditary traits One of these varieties, steatopygia,[*] has even become a racial characteristic of certain Negro races Hence we must assume a genetic factor that regulates the regional lipophilia of the subcutaneous adipose tissue

(2) There are various types of obesity caused by disorders of endocrine glands Some of these glands exert an influence upon metabolism and upon the lipophilia of the subcutis Disorders of various endocrine functions occur not infrequently in obese persons and in members of their families Although in the majority of cases such disorders are concomitant rather than causal factors of obesity, this endocrine stigmatization, together with the aforementioned facts, justifies our assumption That is, they are suggestive of an involvement of some endocrine glands in the sphere of activity of the gene complex under discussion To deny the role of these glands in the pathogenesis of obesity[53] is to throw out the baby with the bath

(3) Nervous centers play a dominant role in the regulation of endocrine functions, of local lipophilia, of metabolic functions, and—by mediation of general feelings such as appetite, hunger, satiety, fatigue, etc—of spontaneous intake and output of energy It seems highly probable therefore that these portions of the nervous system are also included in the domain of the genetic factors accounting for the tendency to obesity

One of the misconceptions of modern psychosomatic medicine inheres in the manner in which psychopathologic viewpoints have been applied to the problem of obesity Those who still believe that the problem of obesity is exhausted by the statement that there is an imbalance between intake and output of energy assume that only a particular behavior—the craving for food on the basis of emotional reasons—accounts for overeating and subsequent obesity[54] Do these

authors wish to range obesity as a "behavior problem" among psychiatric instead of metabolic diseases? This would be at least the logical though absurd consequence of their theory I wonder what may have been the emotional reasons for overeating in Christiansen's infants and Danforth's rats (pp 175f)?

Accumulating a definite amount of adipose tissue, and thereby reaching and maintaining a definite body weight, constitute a unitary biologic process controlled by a particular gene or gene complex *The actual manifestation of this gene* complex, however, is spread over a large area of various organs and functions

If the constitutional nature of obesity is taken for granted, the question arises whether anything is known about other genes related to the obesity anlage It was previously mentioned that constitutional obesity in mice has been found to be associated with yellow hair, obviously by virtue of a pleiotropic activity of the same dominant hereditary factor Anything similar is unknown in human obesity

In an earlier part of this book the *Laurence-Moon-Bardet-Biedl syndrome* was mentioned as an instance of linkage of genes It consists of an association of obesity with polydactyly and frequently syndactyly, retinitis pigmentosa, hypogenitalism, abnormalities of the skull (usually oxycephaly), deficient intelligence, and occasionally other degenerative stigmata Not all of the signs are found in all cases, and a dissociation may occasionally be found in several members of one family

In a case under my observation that was reported by Pool,[11 15] extreme familial obesity in a 12-year-old girl was associated with polydactyly, syndactyly, hypophalangism due to an abnormal fusion of the phalanges, a marked congenital deformation of the skull classified as acrocephaly, and intellectual deficiency At birth the girl had a weight of 6 Kg (13 2 pounds) This fact alone justifies considering the adiposity as constitutional It fits into the picture of Christiansen's

"macrosomia adiposa congenita" At the age of 12 years the weight was 182 Kg (400 pounds), the height 157 cm Two brothers of the mother had a body weight of 160 Kg (352 pounds) each, a third weighed 110 Kg (242 pounds)

Another syndrome in which obesity is the leading sign is *Morgagni's syndrome*, which is characterized by the combination of obesity with a peculiar hyperostosis frontalis localized on the inner surface of the frontal bone, and by some signs of virilism, such as hypertrichosis in females In some cases mental disorders are to be found There are also atypical sets of signs, belonging to the Laurence Bardet as well as to the Morgagni syndrome Van Bogaert and Borremans[11] described a family whose members were affected with obesity, retinitis pigmentosa, brachydactylism, and frontal hyperostosis Hyperostosis frontalis interna is a constitutional degenerative stigma that may or may not occur in combination with obesity or other genetically determined abnormalities Its occurrence in many cases of Albright's syndrome was mentioned in a previous chapter I saw such hyperostosis associated with extreme obesity in two sisters Obesity was also present in other members of the family One of the sisters had an enlarged sella turcica Cases of insanity and epilepsy occurred in several other members of this family This shows that only the genetic concept of Morgagni's syndrome can fit the facts This view was recently confirmed by extensive studies of Campos[85] and of Grollman and Rousseau,[91] who report several cases of hereditary occurrence of Morgagni's syndrome The term "metabolic craniopathy" applying to frontal hyperostosis has no justification

2 Essential (Constitutional) Hypertension

Almost the same situation as that existing in obesity is encountered in essential hypertension There are leading authorities in this field who believe that the term "essential" is preliminary only—that it is a confession of our ignorance and

authors wish to range obesity as a "behavior problem" among psychiatric instead of metabolic diseases? This would be at least the logical though absurd consequence of their theory I wonder what may have been the emotional reasons for overeating in Christiansen's infants and Danforth's rats (pp 175f)?

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various reasons, represents but one variety of symptomatic hypertension

In the vast majority of cases of permanent arterial hypertension, such a symptomatic character of the illness cannot be detected, its point of origin is found neither in the endocrine or the nervous system nor in the kidney. Hence the term essential hypertension should be replaced by the term constitutional hypertension, since heredity has been proved to be the causal or at least the foremost causal factor. Statements to the contrary are based on investigations by inappropriate methods[89]

Thus we know *why* permanent hypertension develops in members of certain families. Yet we wish to know also *how* it develops, and which structures and functions of the body are involved, and how they are altered if the abnormal gene or gene complex becomes operative

Is it not an amazing phenomenon that a normal human individual is endowed with a most precise and delicate device that secures the proper adjustment of blood pressure to variable demands for blood flow in local portions of the body? Does this device not guarantee the approximate maintenance of blood pressure in spite of most frequent alterations of some of its components? The integrative mechanism adjusting the peripheral vascular bed as a whole to the physiologic demands of daily life and to occasional extraordinary turmoils is ensured by the normal constitution of the individual, that is, by the presence of a gene or a gene complex governing this device. It implies (*a*) a normal elasticity and normal reactivity of the arteriolar (and more generally, vascular) walls to nervous and humoral stimuli, (*b*) a normal function of the involved parts of the nervous system, composed of the afferent nerves, particularly the so-called blood pressure moderators (carotid sinus nerve and depressor nerve), the bulbar, the superposed diencephalic and the higher cerebral as well as the lower spinal centers and tracts, and the efferent autonomic vasocon

that in the future it will be replaced by exact terms indicating more accurately the nature and mechanism of this illness

Arterial hypertension—like obesity—can be produced by diseases of the endocrine system, such as tumors of the suprarenals or the pituitary gland Both arterial hypertension and obesity can be brought about by experimental lesions or spontaneous pathologic processes of certain portions of the central nervous system These varieties of both arterial hypertension and obesity should be called symptomatic, as contrasting with those types in which the above named pathogenic factors, endocrine or nervous, are not to be detected

In arterial hypertension an additional pathogenic factor is to be taken into consideration, namely, the role of kidneys The ingenious experiments of Goldblatt and his followers have brought to the fore anew the old concept of the renal origin of hypertension The humoral mechanism of this type of hypertension has been proved by the extensive experimental work done in this country in recent years It was surmised years ago by Volhard and his school Many scientists and clinicians were so impressed by this work that they tried to adapt all cases of arterial hypertension of unknown pathogenesis to the renal theory This became a sort of bed of Procrustes Essential hypertension was simply identified with renal hypertension, as failure to demonstrate any signs of renal incompetency would not preclude slight arteriolar changes of the kidney It has been pointed out elsewhere[11] why such a view cannot be sustained Arteriolar changes are the consequence rather than the cause of high blood pressure, although they may create a vicious cycle maintaining and aggravating arterial hypertension This order of events has recently again been proved by negative biopsies of the kidneys in cases of essential hypertension [59] The renal type of hypertension, as it occurs in glomerulonephritis, some cases of advanced chronic pyelonephritis, cystic kidney, increased back pressure caused by urinary retention in the pelvis for any of

ciency undoubtedly concerns more than one particular part of the complicated regulating device composed of precisely co-ordinated nervous and hormonal functions

The abnormal gene accounting for constitutional hypertension is as a rule a dominant characteristic The studies of Hines,[10] carried out on a large scale and using the "cold pressure test to detect predisposed individuals, present strong evidence in favor of this assumption It stands to reason that the frequency of constitutional hypertension varies in different races[17] It is particularly high in the American Negro[15, 18] With the aid of the cold pressure test a greater frequency of hyperreactors, that is, of the constitutionally predisposed, has been found among the Negro as compared with the white population[19] It has been pointed out[15] that genetic rather than environmental factors must account for this fact

What is generally known as malignant hypertension is also more frequent in Negroes than in whites In Negroes the malady takes a more rapid downhill course, and death occurs at an earlier age than among whites It is the *involvement of* the kidneys by arteriolar fibrosis and necrosis that causes the malignant course of the disease This renal pathology is actually the result of high blood pressure It seems therefore *as though* the structural reaction of the arterioles to elevated blood pressure were also dependent on a constitutional factor Although the exact genetic mechanism is not known, the involvement of the effector organ, that is, of the arterioles, in the sphere of action of the pathologic gene or gene complex is evident

The enlargement of the adrenal cortex in cases of essential hypertension[5, 16] *is* an important fact, suggesting the participation of the adrenals in the pathogenesis of hypertension Histologic signs of hyperactivity of the adrenal medulla, though nonspecific, were recently found in essential hypertension[14] In a remarkable case reported by Thorne et al,[37]

strictor and vasodilator nerves, (c) proper and adequate liberation of hypertensive and perhaps hypotensive hormones, which in turn depends on a normal function of certain endocrine glands, chiefly the suprarenals, and their prompt and adequate response to nervous and perhaps humoral stimuli These are only the main principles involved in the integrative mechanism securing a relative constancy or homeostasis of *blood pressure*

This is again an instance of what we called the principle of treble safeguard. the homeostasis of the blood pressure is guaranteed by the cooperation of the effector organ (the blood vessels) and of the nervous and the hormonal regulation It is a highly intricate mechanism, its integrative character, however, is preserved by a special gene or gene complex governing this unitary biologic process

This gene or gene complex seems liable to alterations in two opposite respects, thus representing an example of multiple allelomorphism One alteration of the "blood pressure gene" consists in maintenance and regulation of the blood pressure at an abnormally low level This is the genetic background of what is clinically known as *constitutional hypotension* Such a familial condition is actually a harmless constitutional variation rather than a disease and as a rule does not require any treatment The other, far less harmless alteration of the blood pressure gene leads to a progressive elevation of the blood pressure that eventually becomes inconsistent with health and, by virtue of its consequences with regard to the anatomic structure and function of various organs, with life

We are able to recognize the presence of such a constitutional predisposition to hypertension by certain tests Excessive response to pressor stimuli such as cold, muscular exercise, adrenalin injection, or smoking may indicate future development of constitutional hypertension These tests demonstrate an insufficiently stabilized mechanism for securing the maintenance of a constant blood pressure level This insuffi

reasonably be concluded from the facts known to date with regard to the constitutional background of blood disease.

a) PERNICIOUS ANEMIA AND IRON DEFICIENCY ANEMIA

Since we have gained better knowledge of the pathogenesis of pernicious anemia and of effective treatment of it, the term pernicious has become obsolete and incorrect. The facts pertaining to the constitutional etiology of this malady were critically surveyed in 1936 by K. E. Paschkis.[21] Pernicious anemia occurs far more frequently in several members of the same family than would be expected from pure coincidence.[27, 61] Remarkable in this respect is a report of Maclachlan and Kline.[23] In the family concerned, both parents, who were first cousins, suffered from pernicious anemia. Three of their four children developed the same disease, the fate of the fourth child was unknown, as he was not heard of after leaving his home town at an early age. Askey[61] observed 5 cases of pernicious anemia in thirteen children in one generation. Several instances of pernicious anemia in identical twins are strong evidence for heredity as an etiologic factor.[11]

Gastric achylia is to be detected frequently in relatives of patients suffering from pernicious anemia. These relatives need not present any signs of blood disease. The failure to secrete hydrochloric acid may or may not be associated with failure to produce the intrinsic pernicious anemia factor, it is, however, indicative of a biologic inferiority of the stomach, constitutional in origin, as is suggested by its hereditary occurrence. One genetic factor operative in the etiology of pernicious anemia must, therefore, affect the stomach. According to the most probable theory today,[21] this factor cooperates with another gene, pertaining to the reactivity and biologic value of the bone marrow.

There have been reports on many families whose various members were suffering either from pernicious anemia or hypochromic, that is, *iron deficiency* anemia. In exceptional cases,

persistent hypertension was cured by surgical removal of a pheochromocytoma. Essential hypertension ran in the patient's family. Did this patient, who was said to have been surgically cured, represent a case of symptomatic or of essential hypertension, only precipitated in its course by the adrenal tumor that had developed in one of the organs ruled by the abnormal gene?

Menopause or, less frequently, diseases of the thyroid may or may not coincide with the first clinical manifestation of constitutional hypertension. They act, however, merely as accelerating or aggravating and not as direct causal factors. They may unleash the actual manifestation of a latent constitutional predisposition to arterial hypertension.

The problematic correlation between body build and blood pressure has been discussed in the preceding chapter. Another peculiar correlation, between blood pressure and a particular psychologic trait, was casually detected by statistical studies of the large material available to life insurance companies.[20] It was found that persons with low systolic blood pressure commit suicide most frequently. Suicidal tendency increases with decrease of pulse pressure, that is, with relative rise of diastolic pressure. High systolic with low diastolic pressures give the lowest suicide ratio.

3. *Diseases of the Hemopoietic System*

Maintenance of the normal number of circulating blood corpuscles—erythrocytes, leucocytes, and thrombocytes—is secured by proper function of the hemopoietic system and its regulation by the endocrine and nervous system. The rate of production and liberation of new cells parallels exactly the rate of their continuous destruction. Disorders of this precise cooperation of various organs may originate in any of them. It is not intended to enter into a discussion of those endocrine and nervous alterations that result in an abnormal composition of the blood. Attempt is made only to point out what can

disintegration of the conglutinated red cells Hemoglobin is set free and transformed into blood pigment, to be found in various organs, and into bilirubin, to be found in increased amounts in the blood serum The disintegrated red corpuscles and shadows finally disappear as a result of the phagocytic action of the reticulo-endothelial cells, which are seen in full activity and proliferation in the spleen, liver, bone marrow, and lymph nodes

How the constitutional trait of *ovalocytosis* or *elliptocytosis*, that is, of elliptic erythrocytes, may in certain cases produce hemolytic anemia, is unknown The osmotic resistance of the elliptic cells is not diminished [a] [b]

Related to these types of hemolytic anemia is Cooley's *erythroblastic* or *Mediterranean* anemia,[c] or thalassemia,[d] about which we have been enlightened chiefly by recent studies of Dameshek [e] He uses the term "familial Mediterranean target-oval cell syndromes," because so-called target and oval red cells in abnormally high number represent the main characteristic sign of a constitutional state that is transmitted usually as a dominant mendelian characteristic in certain families of Greek, Italian, or Syrian extraction There is a descending scale, beginning with the rare full fledged and fatal Cooley's anemia and leading to various more frequently encountered and less serious hereditary syndromes that present as their common denominator a hemolytic hypochromic anemia with abnormalities of the red corpuscles that include the presence of target cells, oval cells, stippled cells, increased resistance of the cells to hypotonic solutions, and complete refractoriness to iron therapy At the lower end of the scale are individuals without anemia or evidence of other abnormalities, but showing an increased number of target and oval cells Target cells are unusually thin mature red corpuscles, and it may be well to call this state *leptocytosis* The cause of the increased hemolysis (icterus, splenomegaly) in leptocytosis is unknown Hypothetically it is explained by Dameshek as the result of the

the patient may have had such an iron deficiency anemia for years, later developing the classic pernicious anemia[63] Iron deficiency anemia has been repeatedly reported as occurring in several members of a family, and its constitutional basis in such cases is probably to be found in an abnormality of the bone marrow As a matter of fact, various factors other than this constitutional one may be operative or cooperative in the etiology of iron deficiency anemia[24] To say more about the underlying genetic factors of this and the "pernicious" type of anemia would be unjustified speculation According to Draper, patients affected with pernicious anemia tend in their measurements markedly to approach the acromegalic type This statement requires confirmation on a larger scale It does not accord with my own experience

b) HEMOLYTIC ANEMIAS

There are several types of abnormally shaped erythrocytes, constitutional in origin, that may be merely harmless curiosities, they may, however, lead to anemia and jaundice, hemolytic in nature *Sicklemia* or *drepanocytosis*, *ovalocytosis*, *leptocytosis*, and *spherocytosis* represent conditions that are merely constitutional aberrations but involve a specific predisposition to a particular disease The pathogenic mechanism of the hemolytic anemia and jaundice resulting from sicklemia, ovalocytosis, leptocytosis, or spherocytosis is different in each type

The most satisfactory explanation of hemolytic anemia resulting from the *sickle cell trait* seems to be the following[25] The abnormal configuration of the erythrocytes, which are greatly elongated, pointed, curved, and bizarrely shaped, causes stagnation and conglutination of these cells in the small blood vessels of various organs Engorgement with disfigured blood corpuscles is to be observed in the distended capillaries of the spleen, liver, lymph nodes, lungs, kidneys, and other organs Stagnation of the capillary circulation leads eventually to

affected by the pathologic gene that must be considered the etiologic factor in the ailment? In full accordance with the general principles of genopathology, it has been assumed[1, 26] that it is the duration of life of the red blood corpuscles that is guaranteed by a gene, this gene therefore extends its action upon the structures and functions that are responsible for the duration of life of the red corpuscles It seems that both the structure of the red corpuscles and the function of the spleen depend on this particular gene If the life span of erythrocytes ranges between three and four weeks under normal conditions, this time is shortened in cases of hemolytic jaundice

The abnormal gene that accounts for such a shortening of duration of life of the red blood corpuscles brings about the constitutional predisposition to the disease, not the disease itself Enlargement of the spleen, increased fragility of the erythrocytes, urobilinuria or increased bilirubinemia, may indicate an abnormally high rate of destruction of erythrocytes in healthy members of families carrying this abnormal gene As long as the bone marrow and the liver are able to make up for the excessive destruction of red corpuscles, there is neither anemia nor jaundice If, however, the bone marrow fails to produce new erythrocytes at the required higher speed, and if the liver fails to dispose of the excessive amounts of liberated hemoglobin, the clinical picture of hemolytic anemia with icterus develops Thus it is the functional reserve power of both the bone marrow and the liver that determines whether or not the actual disease, or a compensated state indicating merely the constitutional predisposition, results from the presence of the pathologic gene

Heredity is usually dominant in all these varieties of constitutional hemolytic anemia, that is, in sickle cell anemia, in ovalocytic and leptocytic anemia, and in hemolytic icterus Cooley[11] considered the possibility of regarding them as an instance of multiple allelomorphism, that is, that they may represent different mutations of the same gene

breakdown of unused precursors of hemoglobin The red cell count may even be abnormally high, owing to a compensatory tendency of the bone marrow The term "erythroblastic anemia" should be abandoned, as it does not indicate any specific characteristic Leptocytosis is merely a constitutional abnormality, not an actual disease Yet it involves the predisposition to a serious, frequently fatal disease

Spherocytosis with resulting microcytosis is the characteristic feature of what is known as familial, or better, *constitutional hemolytic jaundice* Spherocytosis is today considered a precursory stage of hemolysis Spherocytes show diminished osmotic resistance There is strong evidence that both increased fragility of the red corpuscles and increased activity of the spleen are operative factors in excessive hemolysis with subsequent anemia and jaundice This is substantiated by the following facts Splenectomy is the treatment of choice in cases of constitutional hemolytic jaundice, although relapses may occur after varying periods of time The curative effect of splenectomy in most of the cases indicates that in the pathogenesis of this ailment an essential role is played by a hyperactive spleen On the other hand it must be assumed that abnormal red blood corpuscles with increased fragility and tendency to hemolysis are produced by the bone marrow This is to be inferred from the fact that spherocytosis and diminished osmotic resistance of the erythrocytes usually remain unchanged after successful splenectomy Furthermore, the assumption is borne out by the experiments of Dacie and Mollison[64] They found the survival of normal blood transfused into 6 patients with familial hemolytic anemia to be normal, whereas blood taken from a patient with hemolytic anemia, both before and after splenectomy, disappeared rapidly when transfused into a normal recipient

There has been much debate on the question as to whether a constitutional abnormality of the erythrocytes or a constitutional hyperactivity of the spleen accounts for the excessive hemolysis In other words, which organs and structures are

autopsy revealed, besides the typical microscopic features of Hodgkin's disease, caseous tuberculosis of some lymph nodes, and in addition, in one group of mediastinal lymph nodes, the characteristic signs of lymphosarcoma. Does not such an occurrence hint at a particular morbid predisposition of the lymphatic tissue—does it not indicate a biologic inferiority of this tissue, since it was affected with three anatomically different pathologic processes at the same time? Would it not be worth while to concentrate our attempts on study of the peculiar reactivity of the affected individual, and particularly of his lymphatic tissue, rather than solely on discovery of a specific pathogenic micro-organism?

Is not the same consideration justified with respect to what is known as *sarcoidosis*, Besnier-Boeck-Schaumann disease, or lymphogranuloma benignum? The etiology is unknown, but a relation to Koch's bacilli seems to exist in the same way as in Hodgkin's disease.[21, 22]

Constitutional morbid predisposition due to biologic tissue inferiority of the lymphatic elements is suggested particularly by the experience with a comparatively newly recognized form of disease involving the lymph nodes and spleen. It has been designated as "generalized giant follicular lymphadenopathy," "follicular lymphoblastoma," or Baehr-Brill-Symmers disease.[16, 17] According to Siebert[17] this disease may have a benign character or may undergo direct transformation into

(*a*) A polymorphous cell lymphosarcoma, or (*b*) it may become associated with histologic changes of Hodgkin's disease or (*c*) with the changes of lymphatic leukemia or (*d*) with those of apparently unique disease, characterized among other things by necrotic lesions in the lymph node follicles and spleen and lastly (*e*) the combination of giant follicular lymphoblastoma with polymorphous cell lymphosarcoma and Hodgkin's disease may be observed in the same lymph node.

These facts are in my opinion a cogent hint regarding the constitutional background of the different varieties of lymphadenopathy.

c) ERYTHREMIA AND LEUKEMIA

There are families in which several members may show abnormally high erythrocyte counts and hemoglobin values. This condition is known as congenital, familial, or benign *polycythemia* or *erythremia*[1,28] It does not seem that such cases are essentially different from those of the usual type of Vaquez's disease,[28] except for their early onset and benign character. In a case of erythremia vera reported by Gutzeit,[1] the son of the patient developed lymphatic leukemia. Whether or not this was pure coincidence, there is no doubt that both erythremia and the various types of *leukemia* arise from a particular constitutional basis, that is, that abnormal genes are at least cooperative etiologic factors. Leukemia has frequently been reported to have affected several members of the same stock. Recently cases of chronic leukemia were reported in three sisters.[65] Two of them had lymphatic, the third myelogenous leukemia. The hereditary character of leukemia in mice permits a more thorough and experimental study of the genetic basis of the disease.

d) HODGKIN'S DISEASE

The etiology of Hodgkin's disease is unknown. It is even controversial whether this disease should be considered as an infectious granuloma or a neoplasm. There is no evidence of hereditary predisposition to this disease. Recently a report was published[29] on two pairs of identical twins, only one of whom in each pair was suffering from Hodgkin's disease, whereas the other twin was free. Incidentally, the identical character of the twins is not evident from the publication. On the other hand, the mother of one of the pairs of twins had also suffered from Hodgkin's disease. It is certain that at least in many cases there is no relation whatsoever to tuberculosis. In some cases particular germs were found and believed to be the etiologic factor.[1,30] I mentioned a case having the clinical picture and course of Hodgkin's disease; the

autopsy revealed, besides the typical microscopic features of Hodgkin's disease, caseous tuberculosis of some lymph nodes, and in addition, in one group of mediastinal lymph nodes, the characteristic signs of lymphosarcoma Does not such an occurrence hint at a particular morbid predisposition of the lymphatic tissue—does it not indicate a biologic inferiority of this tissue, since it was affected with three anatomically different pathologic processes at the same time? Would it not be worth while to concentrate our attempts on study of the peculiar reactivity of the affected individual, and particularly of his lymphatic tissue, rather than solely on discovery of a specific pathogenic micro-organism?

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e) HEMORRHAGIC DIATHESES

Constitutional abnormalities of the *thrombocytes* are concerned in various types of hemorrhagic diathesis *Hemophilia*, according to investigations of recent years, is due to a lack of thromboplastin [33, 34] The relatively smaller amount of thromboplastin in hemophilic blood is explained by an abnormal stability of hemophilic blood platelets, *since the thromboplastin of normal blood is derived from continuous disintegration* of the blood platelets in the circulation The thrombocytes of hemophilics may even be increased in number; they agglutinate promptly and are more resistant to hypotonic solutions as compared with thrombocytes of normal persons; also, they resist, in abnormal fashion, physiologic disintegration in the body, and therefore account for the insufficient supply of *thromboplastin in hemophilic blood, with the subsequent* retardation of blood coagulation and failure of proper thrombus formation As the thrombocytes originate in the cytoplasm of the megakaryocytes, hemophilia was defined as "essentially a congenital dysfunction of the megakaryocytes "[34]

It is generally recognized that this abnormality of the blood platelets and megakaryocytes respectively is caused by one pathologic gene that is located in the x-chromosome Hemophilia *is the most characteristic instance of* sex-linked *inheritance* in humans There is unanimity too concerning the recessive character of the abnormal gene It was moreover demonstrated by Berta Aschner[35] that there are quantitative differences in the abnormality In the mildest form, the abnormal gene may cause only the features of hemophilia that can be detected by laboratory examination of the blood, clinical manifestations of the latent disease may be absent even in men carrying the abnormal gene On the other hand, the intensity of action of the abnormal gene may occasionally be so great as to produce the hematologic signs, and in exceptional instances even some tendency to excessive bleeding, in heterozygous female carriers of the pathologic gene This

interpretation of clinical facts is in accordance with the view that dominance and recessiveness of a gene are terms of relative value only The power of penetration of a gene that accounts for its dominance or recessiveness may vary and depends also on the power of its allelomorph

What is known as *hereditary pseudohemophilia* is an entirely different disease, although the blood platelets are also involved The coagulation time of the blood is normal but the bleeding time is prolonged—exactly the reverse of the manifestations characterizing hemophilia Both males and females may be affected and the possibility of direct transmission by either to the next generation clearly distinguishes the condition from hemophilia It was shown by Aschner[34] that the different varieties of this condition described as *thrombopenic purpura, hereditary hemorrhagic thrombasthenia* (Glanzmann), *hereditary thrombopathic purpura* (Willebrand and Juergens), represent essentially the same pathologic process Neither clinically, hematologically, nor genetically does a separation of these conditions seem to be justified The essential abnormality in all these varieties is an insufficient agglutination of the blood platelets, which also frequently exhibit morphologic abnormalities such as variations in size, shape, structure, and staining This abnormality of the thrombocytes accounts for the insufficient thrombus formation and protracted bleeding when a leakage from a blood vessel occurs Temporary diminution of the number of the circulating thrombocytes is frequently observed in the affected persons As a matter of fact, such a phase of thrombopenia causes a hemorrhagic crisis, and at this time the case is diagnosed as one of thrombopenic purpura

The etiologic factor in the different varieties of hereditary pseudohemophilia is an abnormal gene or gene complex that is usually transmitted as a dominant characteristic The theory of a sex linked character was rejected by Aschner

The comparison of true hemophilia and pseudohemophilia

is of great interest. Both diseases are due to hereditary abnormalities of the blood platelets. These abnormalities, however, are different in nature, in their genetic origin, and in the resulting clinical pictures. In hemophilic persons the blood platelets do not disintegrate as readily as in normals and therefore the thromboplastin that is necessary for normal coagulation of the blood is deficient. In pseudohemophilia the blood platelets liberate normal amounts of thromboplastin and the blood coagulates normally; they do not, however, conglutinate and thereby initiate thrombus formation stopping a leakage of blood vessels. In addition, the rate of regeneration of thrombocytes may temporarily lag behind the rate of their destruction. The gene causing hemophilia is located in the x-chromosome and is recessive; the gene causing pseudohemophilia is located in an autosome and is as a rule dominant. There is no relationship between these two pathologic genes and their phenotypical manifestations,[35] except for the fact that both act upon the same body structure, the thrombocytes.

There is a type of hereditary hemorrhagic diathesis that seems to be due to a selective defect of one particular function of the liver. It is known as *idiopathic hypoprothrombinemia*.[77,78] This condition does not yield to vitamin K therapy. In Giordano's case[77] it was found in both parents and three siblings.

We have not attempted to discuss here another type of constitutional hemorrhagic diathesis, Osler's hereditary telangiectasis, as it is due to a genetic failure of the vascular rather than of the hemopoietic system. The two failures, however, were found combined in a family in which hereditary hemorrhagic telangiectasis and elliptocytosis were detected in four generations. Various members of this family were affected with both or one or the other of these genetic abnormalities.[82]

It is interesting, however, that there is found in swine an inheritable bleeding disease, transmitted as a simple recessive

mendelian characteristic, the pathogenic mechanism of which involves both a coagulation defect and a blood vessel defect.[18] The coagulation defect is associated with a failure of the injured blood vessels to undergo normal constriction. This is again an excellent illustration of a biologic unit ruled by one gene that extends its action upon morphologically different structures, such as the cellular elements of the blood and the blood vessels. Prevention of hemorrhages resulting from inevitable minute daily injuries is secured by proper cooperation of these different structures. Biologically and genetically, prevention of such hemorrhages is a unit, anatomically and functionally, however, this unit consists of a rather complex mechanism.

4 Peptic Ulcer

Peptic ulcer of the stomach or duodenum results from destructive action of the gastric juice on the mucous membrane. What accounts for the lower resistance of the affected area of the gastric or duodenal wall? Numerous theories have been advanced in this respect: hematogenous infection, inflammatory condition of the mucous membrane, impaired blood supply for any of various reasons, are supposed to facilitate autodigestion of the living tissue. A lowered blood supply may be caused by embolism, thrombosis, organic lesions of blood vessels, and particularly by vascular spasms or by spastic contractions of the gastric muscle, pinching and compressing the small blood vessels. These spastic conditions of the arteries or gastric muscle fibers result from abnormal irritation of the autonomic nervous system.

As a matter of fact experimental ulcers can be produced in laboratory animals by lesions of both the vagus and the sympathetic nervous system and by drugs acting upon the autonomic system. Cerebral diseases, particularly those affecting the region of the fourth ventricle, were occasionally observed in association with peptic ulcer and gastric hemorrhages

Hyperacidity of the gastric juice, untimely gastric secretio lack of mucous secretion, chemical and thermic action of foo stuffs, toxic action of nicotine and other poisons, were claime to facilitate the production of peptic ulcer With some justi cation, peptic ulcer has been included in the sphere of psych somatic medicine in recent years, and even endocrinology h touched on the problem of peptic ulcer, since treatment wi parathyroid hormone, estrogen, and anterior pituitary lo extract has been recommended

None of these theories is wrong but each is valid only so f as a particular group of cases is concerned Peptic ulcer fo lowing a severe burn or arising from an arteriosclerotic conditio of the gastric arteries has nothing to do with a hyperirritab vagus, and most cases of peptic ulcer are no more psychos matic problems than are various other organic diseases It wa pointed out in a previous connection (p 48) that heredity is a important etiologic factor in peptic ulcer It was shown th this factor can be only a constitutional biologic inferiority the stomach and duodenum, respectively, as the hereditar predisposition includes peptic ulcer, cancer of the stomach, an various types of chronic nervous indigestion Even the clin cal picture of ulcer, and its location in the duodenum or i the stomach, may be similar in several members of the sam family I know three brothers affected with duodenal ulcer two of whom developed a "covered perforation" that pre sented exactly the same anatomic picture at operation I kno another family in which profuse hemorrhage occurred as th first and chief symptom of peptic ulcer in a young physician his younger brother, and two of his uncles on his mother's side In one of the uncles the hemorrhage was fatal Th mother died a few years later of cancer of the stomach Case of peptic ulcer occurring in identical twins have occasionall been reported [1, 79] The accompanying pedigree of an ulce family illustrates particularly well the development of ulce in two children whose parents both also had ulcer (fig 4)

As previously mentioned, our studies on 255 cases of peptic ulcer showed the following If both parents of an ulcer patient were free of any stomach trouble, 10 8 per cent of their children developed ulcer If one of the parents had some kind of chronic stomach disturbance, 25 7 per cent of their children suffered from ulcer

From these figures the conclusion was drawn that the con stitutional predisposition to peptic ulcer is probably a simple recessive mendelian characteristic Of course such an in herited constitutional predisposition does not mean presence of the disease itself, the disease will break out only if some

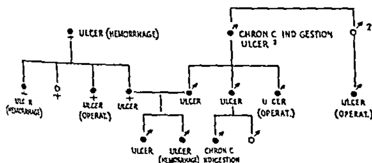


FIGURE 4

other intrinsic or extrinsic conditions are fulfilled, all of them cooperating to produce the disease It follows from our previous statements that these cooperating causal factors are at work in only about 50 per cent of all constitutionally pre disposed persons According to the mendelian laws, the figures in our series would have been 25 per cent and 50 per cent respectively, instead of 10 8 per cent and 25 7 per cent, if every predisposed person had really developed ulcer

What are these intrinsic or extrinsic factors, other than the constitutional weakness of the involved organ, that may be considered cooperative in the etiology of peptic ulcer? They are precisely the conditions enumerated previously, the

conditions regarded as playing a role in the causation of peptic ulcer Neuropathic constitution with its hyperirritable autonomic nervous system is probably the most common and important one Transition of chronic nervous indigestion to actual peptic ulcer is not an uncommon occurrence, and the modification of the clinical picture of peptic ulcer by a concomitant neuropathic temperament has been referred to previously (p 128) We must bear in mind that in peptic ulcer, as in most other diseases, not a single cause but multiple cooperating factors must be assumed to represent the etiology One of these factors, and apparently the paramount one, although largely ignored, is, *so far as peptic ulcer is concerned, the constitutional* biologic inferiority of the stomach and duodenum

Contrasting the situation in peptic ulcer with that encountered in pernicious anemia, it might be well to accept, at least *provisionally, the theory of* Paschkis[21] *The normal structure* and function of the stomach is provided for by two genes A failure of either would result in what we call biologic inferiority of the organ An alteration of one of these genes would account for the variation predisposing to peptic ulcer, an alteration of the other gene, however, would produce constitutional achylia and represent a factor predisposing to pernicious anemia Both genes are involved in the etiology of gastric cancer, in so far as they determine the localization of a cancer if this disease develops in a particular individual

5 Cancer

It is strange indeed that there are leading physicians today who reject the theory of inheritability of cancer or, to be more precise, of cancer predisposition Only ignorance of the principles of genetics accounts for the fact that inheritance at best is granted a role in a few exceptional cases of malignancy, whereas this role is denied with respect to cancer in general Tremendous material has been accumulated, both from breeding *experiments in laboratories and from* clinical observa-

tions in man, indicating that inheritable susceptibility to cancer is no longer a matter of belief but a matter of fact [36, 37, 38]

Some rare types of both benign and malignant growths, such as carcinoma of the skin in xeroderma pigmentosum, or glioma retinae (retinoblastoma), are known to occur in several members of a family Some more instances of this kind may serve as illustration Heredity is acknowledged to be an etiologic factor in angiomatosis of both the skin and several inner organs, such as the retina and the cerebellum, in melanotic tumors of the choroid, in dermoids of the ovary as observed by Sippel in three sisters, in glioma of the brain Recklinghausen's neurofibromatosis is considered to behave in certain families as a dominant mendelian characteristic Gardner and Frazier reported the instance of a family spanning five generations and including 217 members, thirty eight of whom suffered from deafness of both ears In seven of these, physical and neurologic examination yielded the diagnosis of bilateral tumor of the acusticus, in two others presence of this lesion was established through autopsy, and several became blind from papillitis (choked disk) The rare malignant embryonal nephroma was observed in two siblings by Fischer-Wasels Juengling reported on a family in which fifteen members in three generations developed rectal cancer on the basis of polyposis intestini Sahler observed the very rare nevus cancer of the vulva in a mother and daughter Considering the rare occurrence of primary cancer of the liver, it can hardly be regarded as pure coincidence that Hedinger observed this cancer in two sisters who were affected within a short time interval Henke reported cancer of the larynx in three brothers, Friedrich, cancer of the lip in a father, his brother, and his son, Warthin, cancer of the lip in four brothers whose parents both had several cancer cases in their families Three of these brothers were smokers, the fourth, who did not smoke, developed cancer at a more advanced age Adenocarcinoma of the small intestine was recently reported in a 43-year-old

father and his 16-year-old daughter.[92] The father's brother had mucous colitis.

Arguments less convincing but nevertheless suggestive of heredity, are afforded by instances of families in which malignant growths of a more common localization occur with conspicuous frequency. One of the best-known examples is the family of Napoleon, who, like his father and three of his brothers and sisters, died of carcinoma of the stomach. Pel saw five of seven children of a certain couple die of cancer of the stomach, and also observed a case in which the grandmother, mother, and three daughters died of carcinoma of the breast. Pemberton operated on a mother, her four daughters, and three nieces for carcinoma. With the exception of 1 patient who had a cancer of the stomach, all 7 patients had cancer of the breast. Three of the daughters later developed second cancers in the other breast. Many cases of similar nature are reported in the literature.

Thus it is evident that in some families there occurs an inheritable tendency not only to certain neoplasms but also to their development in specific organs. Such evidence, however, is only exceptional and in the majority of cases this constitutional tendency is not easily demonstrated. This does not mean that it does not exist. On the contrary, it results from the genetic basis of cancer as we see it; nothing else can be expected. Why this is the case, and why heredity of human cancer can hardly be proved by statistical methods, has been demonstrated.

As far back as 1925 we formulated the following hypothesis,[39] which is in accordance with the known facts: Constitutional predisposition to develop cancer depends on two genetic factors, one representing the general neoplastic tendency, the other accounting for the localization of the tumor in a particular organ or system of organs. It is of secondary importance whether these two abnormal genes are dominant or recessive with respect to their normal allelomorphs. Of paramount con-

sideration is the dihybridous type of hereditary transmission, that is, the dependence on two genes of what we must call constitutional cancerous predisposition. It is most gratifying that exactly the same hypothesis was many years later brought to the fore by Schinz and Buschke,[40] Maud Slye,[41] and White.[42] Statistical studies of both Waaler and Michel[43] also led to the conclusion that two genetic factors are involved in hereditary transmission of cancer.

The hypothesis advanced—as has been pointed out in previous publications[31, 33]—explains the following facts:

(1) If both parents in a family are afflicted with carcinoma of the same organ, from 50 to 100 per cent of their children are victims of the same disease. The percentage depends on whether the two genetic factors are dominant or recessive. One such instance may serve as illustration. Paulsen[44] reported on a family in which both parents died of gastric cancer. Six of their seven children died of the same disease. The seventh and youngest child was killed in an accident when 28 years of age; he obviously did not live long enough to develop cancer of the stomach.

A recent statistical study of cancer among inhabitants of the Swiss canton of Glarus induced Hanhart[45] to doubt the importance of heredity in the etiology of cancer. It seems to me, however, that Hanhart's interpretation is not conclusive; on the contrary, it speaks in favor rather than in refutation of our concept. In each of thirty-three married couples *in* Hanhart's series, both partners died of carcinoma of the stomach. These couples together had ninety-seven children past the age of 40, but only 11.34 per cent of these had likewise developed cancer of the stomach, and 15.46 per cent of them some type of carcinoma. The exact age distribution of these children is not indicated. According to *Hanhart's* own statistics, the frequency of cancer is twice as great among persons over 60 years of age as among persons between 40 and 60. As to the age group of the ninety-seven children, we know only

that they were over 40 We do know, however, that the general frequency of cancer of the stomach among persons over 40 is far less than 11 34 per cent, and that localization of cancer in the stomach as compared with cancer in general in the whole population certainly is not sufficiently prevalent to explain the slight difference between the two figures 11 34 per cent and 15 46 per cent In other words, Hanhart's statistics demon strate that the children of those couples where both partners died of carcinoma of the stomach had a special predisposition of the stomach to develop cancer How many more of them would have developed gastric carcinoma if they had lived long enough, nobody knows

(2) If the two parents suffer from cancer of different organs, the chances for the offspring are infinitely more favorable—in fact they are not much worse than they would be if only one parent were afflicted with cancer If for instance the parents who both suffer from malignant growths of different site have no other organ susceptibility than that determining the site of the growth, not even in a heterozygous and concealed state, the children may safely be expected to remain cancer free Cancerous children would result from such marriages only if the pathologic organ susceptibility determining the site of the cancer in one parent were also present, at least in heterozygous state, in the other The presence of two or more such organ susceptibilities in combination with a general neoplastic tend ency is the genetic basis of multiple primary malignant tumors in different organs

The incidence of multiple primary cancers is estimated at between 2 and 4 per cent of all malignant lesions [41, 69] Sta tistical analysis of a large autopsy material with regard to multiple primary tumors, both benign and malignant, was carried out by Berta Aschner [42] It substantiated the existence of what French physicians have called *diathèse néoplasique*, in other words, it proved that a general neoplastic tendency actually exists

The 'localization factor' is probably identical with what we have termed biologic inferiority of an organ or system of organs Let us recall what was said about the relationship between peptic ulcer and carcinoma of the stomach Constitutional biologic inferiority of this organ had to be assumed as the common basis of these diseases A similar situation was found to exist with respect to cancer of the colon Statistical studies on 176 patients in proved cases of cancer of the large intestine, as compared with control groups of patients having respectively carcinoma of the kidney and no carcinoma at all, were carried out in the Mayo Clinic by Bargen, Mayo, and Giffin [63] The authors came to the following conclusion When multiple cancers occur in any family and one cancer at least is localized in the colon or rectum, there is an appreciably greater chance that cancers in other members of the family will be localized in the colon, the rectum, and also in the stomach, than there is in cancerous families in which colonic and rectal cancer are not known to exist

In some instances, the constitutional biologic inferiority of an organ as the localizing factor in relation to a tumor may be quite obvious It is known that malformed organs have a particular tendency to develop malignant growths Instances illustrating this fact are Mornard's[37] case of carcinoma of an aberrant mamma located in the axillary region, Schoen's[44] case of lymphosarcoma in the breasts of a gynecomast, cases of carcinoma of the esophagus occurring in persons with idiopathic dilatation of the esophagus,[68] or sarcoma affecting cryptorchid testicles Wells[70] observed a unique case of seminoma that arose from a unilaterally undeveloped genital anlage Developmental abnormalities of the lung were found in cases of bronchogenic carcinoma [71]

(3) Identical (uniovular) twins tend to suffer from the same type of tumor A large body of material pertaining to this problem[37, 44] is available in the literature Various tumors, particularly cancer of various organs, have been reported to

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The outstanding work of C Huggins sheds light upon the influence of sex hormones in carcinoma of the prostate Perhaps also the growth promoting hormone of the anterior pituitary should be taken into consideration in this respect [47] Whether or not something like the "milk factor" in Bittner's[48] mouse strain exists in humans is not known In mouse strains with high susceptibility to breast cancer, there has been discovered an unknown factor, transmitted in the milk, that has a marked influence on this susceptibility The milk of breast cancer stock mothers exerts a "breast cancer-producing influence" on the susceptible animals [49] It seems that in mice not only foster nursing but also the intra uterine environment of foster mothers exerts an influence upon the manifestation of constitutional cancer tendency [51] Fekete and Little[55] transferred ova from a strain of mice with high susceptibility to mammary tumor to a strain with low susceptibility, and vice versa Such transfer of ova into foster mothers produced increase and decrease, respectively, of mammary tumor incidence that was greater than the increase and decrease brought about by foster nursing alone *in these two strains* Descendants of the mice originating from transferred ova, however, did not differ as regards tumor incidence from the corresponding groups of the original animals with transferred ova In other words, the genetic predisposition to mammary tumors remained unchanged

That extrinsic factors such as chronic trauma, chemical, thermic, and parasitic injuries, and X rays and radium may play an [illegible] the [illegible] swee[illegible] so-called Schneeberger lung cancer, the kangri cancer of the Hindus, the skin cancer of radiologists, and the bone sarcoma of radium dial painters The conclusion has been drawn[57] that these extrinsic factors, if acting with considerable intensity over a long period of time, may not only precipitate the manifestation of a latent constitutional predis-

have affected identical twins, frequently even at the same age That this is not always the case, and that only one of the identical twins may suffer from a malignant growth, results from the following facts First, it must be remembered that the presence of the two abnormal genes accounts only for the individual tendency to develop cancer, the actual development of the disease may be precipitated or delayed by extrinsic or intrinsic factors other than these genetic factors Second, tumor formation ranges among those constitutional traits that we may call asymmetric,[78] such as nevi or lefthandedness Concordant appearance of such asymmetric traits is not always to be expected in identical twins [79] Just as cancer of the breast as a rule affects only one breast of a woman so it need not develop in both twins alth[illegible] f the tw[illegible]

of one [illegible] record the case of a family [illegible] bilateral carcinoma of the breast occurred in four generations [80]

Thus it fits [illegible]

in a survey [illegible] comes to the following conclusion. Both twins were affected in a higher percentage of cases in the uniovular series than in the biovular (66 6 and 20 per cent respectively) Moreover, they were affected with the same type of tumor in a greater percentage of cases than were the biovular twins (55 and 20 per cent respectively) This points to heredity as one of the major factors in the determination of the site, the type, and the age of onset of tumors

(4) It has just been mentioned that both extrinsic and intrinsic etiologic factors other than the two abnormal genes may cooperate in the etiology of tumors [81] They may help in the actual realization of a mere constitutional predisposition What are those factors? One such intrinsic factor is probably the hormonal balance, since it is known that the estrogenic hormone exerts a trophic influence upon those female organs that most frequently are involved by malignant growths

had been suffering from constipation When he had an attack of intestinal obstruction he said to his doctor "I think I have cancer of the rectum My father died of it and my mother's sister died of cancer of the duodenum"

The physician scoffed at the idea, gave him a purgative, and dismissed him The patient was never examined and died three months later following an operation for complete obstruction of the sigmoid flexure Of course such a "physician" may be a rare exception today But what is done to see to it that patients of this kind are not taken care of by persons who are not physicians at all, and who are not familiar with facts that, if known, might save a life?

It has been pointed out previously that the *indication for* radical surgical treatment of peptic ulcer should also depend on the family history If peptic ulcer coincides with *an obvious* hereditary neoplastic tendency in the family, there should be no hesitation about gastric resection A pertinent observation was reported to illustrate this situation [11] Phillips[12] observed the following in identical twins Carcinoma developed in the right breast and, eight months after operation, in the left breast of one twin, it is highly probable that both carcinomas were primary Three years later, the second twin had a cancer of the right breast, and two years after, of the left breast Surgical treatment was successful The twins' paternal aunt and their elder sister had also suffered from carcinoma of the breast Ten years after the first appearance of her mammary cancer, the first twin had to undergo an operation for bilateral ovarian papillary adenocarcinoma The question arose What should be the treatment for the second twin? Prophylactic oophorectomy or a course of deep roentgen therapy was considered but, and in my opinion rightfully, not carried out It stands to reason that this individual needs careful periodic examination in order that surgical treatment may be instituted in *time*, but only if necessary

position but perhaps even replace it. They may occasionally create the state of stimulation of cellular proliferation that is produced by genetic factors in the vast majority of cases. The resulting indiscriminate and unchecked growth of the tumor is the same in both eventualities. It should be borne in mind, however, that constitutional and racial factors are important even in the experimental tumors of animals that can be artificially produced by tar products or parasitic infestation. The localization of metastases also may depend on constitutional factors, as was shown by the extensive laboratory experiments of Maud Slye.[37] As a matter of fact, the site of metastasis can also be determined by an acquired weak spot, as we mentioned in a previous chapter (p. 33).

Nothing is known about a correlation between cancer disposition and any other constitutional trait except for one observation recently made by L. C. Strong.[49] Tolerance to the lethal effect of salicylaldehyde in mice has been found to depend on the genetic constitution of the animals. Furthermore, it was observed that this tolerance parallels and therefore may be used as a measure of the intrinsic susceptibility that partly determines the incidence of carcinoma of the mammary gland in mice.

It stands to reason that Strong's discovery throws light on a problem of paramount practical importance—that of diagnosis of cancer susceptibility in man before the actual development of cancer. Unfortunately we lack such a test to date. So far we are forced to draw conclusions from the results of family studies alone. It is beyond question that such studies, carried out with full consideration of the influence of heredity in cancer, can be a valuable aid in early diagnosis. Careful observation and periodic examination of persons who are obviously endangered on the ground of their heredity may save many of them. They should particularly be examined for the type or types of tumor that occur in other members of their families.[50]

Macklin[51] tells the story of a man of 74 who for some years

of an individual, we are able nevertheless to do a great deal for those whose inherited tendencies lead them to undesirable conditions Many malformations due to abnormal genes can be repaired by surgery—as polydactyly or syndactyly, cleft palate, congenital luxation of the hip, up to ligation of a patent ductus Botalli Although we are not able to change genes and to improve deficiencies in the chromosomes, we may alter the environmental conditions that are indispensable or particularly favorable for the actual manifestations of such deficiencies

It belongs to the realm of preventive medicine to guide those who are or seem to be disposed to develop peptic ulcer, diabetes, obesity, essential hypertension, neuroses or psychoses, cancer, etc Regulation of diet, habits, mode of life, advice concerning choice of profession, periodic examination with regard to the individual morbid predisposition, physical and mental hygiene, are the means at our disposal for making up for what nature has denied to certain individuals [1] Those who are suspected of having constitutional predisposition to peptic ulcer should be careful to avoid indiscretions in diet and be modest in consuming strong alcoholic drink and nicotine Those who exhibit a tendency to essential arterial hypertension (on the basis of heredity, cold pressure test, blood pressure varying around the upper limit of the normal value) should avoid physical and mental overstrain, psychic emotions as far as possible, excess in the use of nicotine and strong coffee, they should rest for an hour during the day and for one or two weeks several times a year Overweight should be avoided with particular care It is much easier to prevent obesity originating from a constitutional predisposition than to reduce considerable overweight when it is already fully developed

Frequently the most suitable kinds of life and the most appropriate professions are chosen unconsciously by those whose constitutions deviate from the average in some respect

Allergic states and endocrine disorders, although constitutional in origin, may be amenable to treatment Various

VIII

PRINCIPLES OF TREATMENT, NONSPECIFIC THERAPY, PITFALLS AND ERRORS

1 Principles of Treatment

If constitution comprises all traits and characteristics of an individual that are potentially determined at the moment of fertilization, if constitutional pathology is not more than the pathology of genes, what then is the practical value of studying constitution, since there are no means of influencing chromosomes and genes by therapeutic measures? The ultimate aim of medicine is successful treatment of ailments If ailments are caused, entirely or partially, by abnormal genes, and if there is no hope of mastering these genes, of what use is constitutional pathology to physicians? Does it not hamper rather than enhance our therapeutic attempts, does it not create fruitless pessimism and therapeutic nihilism? Such criticism is frequently heard from those who practice medicine as a craft, and not as a science and art

(1) Whatever the consequences may be, medical science must discover the facts We must face the truth and nothing but the truth, whatever the therapeutic prospects resulting from it may be Furthermore, the medical student must be familiar with all facts pertinent to the understanding of human nature and human disease, whether or not these facts have any direct bearing on treatment Many facts taught and included in the preclinical curriculum have no such relationship

(2) Although genetic factors represent the unchangeable fate

gent psychotherapy in many apparently hopeless cases. Therapeutic results obtained by different varieties of cult medicine and by any mingling of religion with medicine are to be credited to the psychologic factor in therapy. This is one type of what we have called larvated or disguised psychotherapy. What matters from the standpoint of constitutional pathology, however, is the fact that physicians should avail themselves of this powerful method of treatment in many more patients than is commonly thought necessary today. The clear concept of individual constitution is the basis of psychosomatic medicine, in so far as it demonstrates the inseparable unity of body and mind.

That many cases of "fibrositis" or "nonarticular rheumatism," myalgia, neuralgia, and the like, are psychologic rather than physical problems has been known for some time.[2] The mechanistic trend in medical education, and the failure of academic medicine to indicate the need for a simple psychologic approach as a supplement to physical and laboratory examination in all patients, accounts for the fact that modern physicians are obliged to learn about the true situation from recent publications.[2,3] One might agree on applying the term "psychosomatic rheumatism" in the particular cases, but is the qualification "psychosomatic" a privilege of rheumatism? Is it not almost the rule that patients afflicted with compensated organic heart disease suffer from neurotic rather than organic symptoms, if they suffer from the latter at all? *Willius*[4] recently drew attention to this important *problem*. "*The* prompt recognition on the part of the physician that *he is* dealing with two conditions is obviously important, and *unless* the distinction is clearly made, he unwillingly may *perpetuate* the symptoms of the neurosis." The science of *medicine* enables the physician to discover the cardiac lesion, the art of medicine has to consider how many of the symptoms presented are the result of fear, anxiety, and uncertainty rather than of the heart lesion.

branches of physiotherapy, and intelligent and sympathetic psychotherapy, are available to relieve the complaints of constitutional neuropaths It is conceivable that those predisposed to heredodegenerative abiotrophic changes of the nervous system may be benefited by vitamin B in doses larger than those required by normal individuals

A normal person regulates his intake and output of energy automatically on the basis of such general feelings as appetite and satiety, and because his glandular and nervous functions are normal A person with constitutional obesity that he wishes to suppress cannot rely on his automatic regulations and must follow a certain regimen that counteracts them In other words, the obese person is forced to eat and drink not what he wants but what his physicians consider useful He cannot rely on his automatic regulations if he wishes to avoid the consequences of his constitutional trait One point, however, must be borne in mind Although the constitutionally obese person may reduce his weight to normal, he nevertheless retains his unfortunate tendency and must therefore follow a regimen indefinitely It is as when a woman with black hair wishes to change this constitutional characteristic She merely dyes the hair, yet she has to do this all her life if she wishes to hide the constitutional hair color permanently

Sometimes the following objection can be heard There is no difference in the treatment of obesity, whether or not its constitutional (hereditary) character is recognized, therefore it is unimportant to be familiar with the latter, the same should be true with regard to other hereditary diseases The correct *aspect of the matter, however, is different The physician* carrying out a treatment must know as much as possible about the etiology, pathogenesis, and consequences of a pathologic state that he is about to treat Otherwise he deserves the title of quack rather than of doctor There cannot be any discussion about this point

It is unnecessary to emphasize the achievements of intelli

predisposed individual by increasing his resistance, vitality, and healing capacity It stands to reason that this type of therapy deals frequently, although not exclusively, with a correction of constitutional deficiencies or abnormalities It tries to make up for what nature may have refused to certain individuals Appropriate regulation of work and rest, of physical exercise, and of nutrition are such means of nonspecific preventive therapy, unnecessary for the constitutionally fit, but invaluable for the constitutional weakling in both the physical and the mental aspect

The various types and methods of what is known as *physiotherapy* belong mostly to this category of nonspecific treatment

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muscular apparatus, the circulation, the kidneys, the glandular functions, and the nervous system The responsiveness of both body and mind is likely to be influenced by proper application of physiotherapeutic procedures The value of various spas and health resorts lies chiefly in such a "retuning" (German *Umstimmung*) of the organism Medical authorities of our country frequently complain of the undue reluctance of the medical profession to avail themselves of physiotherapeutic methods[5] It may be well to quote Houston[6] verbatim

> Had massage and physical therapy been developed as they have been developed in Sweden osteopathy and its more illiterate imitation, chiropraxis, probably would have found little foothold To *the laity* who quite generally think of medicine exclusively in terms of treatment, the treatment plans of these cults are contrasted with those of the physician To the lay mind, the physician's treatment is drug treatment it is mind versus drugs, God versus drugs manipulation versus drugs mild drugging versus heroic drugging However strongly it may be protested that treatment as offered by the medical profession is catholic and *comprehensive* the doctor cannot be reckoned entirely blameless for the layman's opinion

There are other methods available also for achieving an alteration of bodily reactions such as vasomotor responsive-

This is entirely true The superimposed neurosis, however, is not a privilege of cardiac lesions It is to a varying degree to be encountered in many diseases Essential hypertension, peptic ulcer, gallbladder disease, pulmonary tuberculosis, and many others are no different in this respect from organic heart disease Instead of speaking of two diseases, the organic lesion and the superimposed neurosis, one should say The symptomatology of the particular organic lesion varies with the individual constitution and particularly with the mental attitude and nervous irritability of the affected person Persons with essential hypertension not infrequently experience symptoms such as headache, dizziness, shortness of breath, or substernal pain for the first time after having been told that they have high blood pressure Such a medical consultation may do more harm than good It is not always advisable to inform the patient about the figures and slight variations of his blood pressure, which he is unable to evaluate correctly This will frequently increase if not produce subjective symptoms Only a selected group of patients will actually profit by frank and tactful discussion of their conditions The art of medicine in these cases consists in giving all necessary advice and taking all necessary measures without frightening the patient and creating an atmosphere of hypochondria This can be accomplished only with a great deal of tact and profound knowledge of human nature

2 Nonspecific Therapy

Psychotherapy, in so far as it is applied in disorders other than purely mental, may be considered one variety of nonspecific therapy This term denotes any kind of therapeutic measure that does not aim at the suppression of a particular disease by killing germs neutralizing poisons, diminishing the functional demands upon or increasing the functional capacity of an impaired organ Nonspecific therapy aims at improvement of the condition of the diseased or

predisposed individual by increasing his resistance, vitality, and healing capacity It stands to reason that this type of therapy deals frequently, although not exclusively, with a correction of constitutional deficiencies or abnormalities It tries to make up for what nature may have refused to certain individuals Appropriate regulation of work and rest, of physical exercise, and of nutrition are such means of nonspecific preventive therapy, unnecessary for the constitutionally fit, but invaluable for the constitutional weakling in both the physical and the mental aspect

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There are other methods available also for achieving an alteration of bodily reactions such as vasomotor responsive-

ness, inflammatory and reparative processes A sudden decisive change of *diet*, such as vegetarian or raw food diet for those who are great eaters of meat, or high protein reducing diet for those who indulge in high carbohydrate fat diet, may bring about such a retuning of body and mind To reduce marked overweight by dietetic means is not only compulsory for hypertensives or cardiacs who may be on the verge of congestive heart failure, it is not only helpful in treating osteoarthritis (arthrosis deformans) in obese persons, but it may bring about a change of the whole personality The same holds true when an undernourished, high strung, hypersensitive, nervous asthenic can be induced to gain a few pounds Sodium free diet has been shown to diminish inflammatory reactions and to counteract water retention in the body Retuning of the organism by means of injections of foreign proteins, other colloidal substances, or sulfur, is in use only in actual diseases

Intelligent use of *endocrine* substances may in certain cases represent a variety of nonspecific rather than of substitution therapy This is the case when, for instance, thyroid medication is used in treating constitutional, nonhypothyroid obesity, or when cortico-adrenal hormone is prescribed for asthenic or neurotic fatigue and exhaustion, or when insulin is injected for the purpose of weight increase

What is known as *rejuvenation therapy* is a typical instance of nonspecific endocrine therapy For several reasons it has become somewhat discredited, yet it undoubtedly deserves more attention than it is commonly given Since we possess reliable and chemically pure gonadal hormones, or substances producing the same effect as gonadal hormones, it is unnecessary to refer to the various surgical procedures recommended by Steinach, Doppler, Voronoff, and others What results from the application of gonadal hormones in elderly persons as well as from stimulation of their own aging gonads is as a matter of fact not an actual rejuvenation These persons do

not become younger and do not live longer They may, however, regain greater strength and activity, greater endurance and vitality, and may lose certain symptoms and signs that are characteristic of old age The sex hormone acts as a powerful tonic in many old people The following case of a 50-year-old man observed in the Policlinic Hospital in Vienna will illustrate the situation

The patient looked as if he were at least 70, and showed all signs of precocious aging—white hair, wrinkled face, loss of teeth, advanced arteriosclerosis, and complete sexual impotence He had mild diabetes and an obstinate arteriosclerotic gangrene of the toes. All attempts to cure the gangrene failed, they included amputation of two toes and Leriche s periarterial sympathectomy performed on the femoral artery Finally vasoligation on one side, and Doppler s operation, that is, painting of the spermatic artery of the other side with isophenol solution, were resorted to. The effect was unexpectedly brilliant The gangrene was checked, the patient regained a vitality that became awkward to his wife, he took up his job as salesman again He died suddenly of coronary occlusion after having enjoyed normal life for two more years

3 Pitfalls and Errors

Many of the pitfalls and errors pertaining to the management of various pathologic states have been mentioned in the previous parts of this book, in so far as they result from ignoring the constitutional principle in pathology with regard to both diagnosis and treatment It has become customary to refer to endocrine disorders, vitamin deficiencies, or allergy when any rare disease of unknown etiology and nature is encountered This is true particularly in relation to such ailments of the nervous system, the sensory organs, or the skin as are actually caused by genetic factors They are frequently misinterpreted because physicians are still reluctant to recognize genes as etiologic factors in diseases Too little is known about them and they represent merely invisible potential energies Endocrines, vitamins, and allergens suit the mechanistic trend of modern medicine better than do genetic factors

Some time ago, cases of albinism in Negroes were reported

in the *British Medical Journal* The author[7] concluded: "Consanguinity and heredity have been noted among the alleged causes of albinism, but its aetiology is obscure Can it be due to a fault in the endocrine system. . .?" This illustrates how vague the conception of heredity is among medical writers There is practically no gland with internal secretion that has not been made responsible for causing otosclerosis Painstaking studies were recently published that led to the statement that there is no reason for attributing alopecia areata to an endocrine disorder[8] Could anybody familiar with the clinical picture of alopecia areata and with endocrine disorders believe in such a theory? Recently R Wagner[11] emphasized the frequency of pseudo endocrine states in childhood and warned against useless endocrine therapy in the case of these constitutional defects He adopts and repeats therewith the author's opinion, with which he has been well acquainted for many years

It is astounding how little attention has been given to the constitutional factor in the etiology of obesity This is particularly true with regard to obesity in children Froehlich's type, or adiposogenital dystrophy, is commonly referred to in the diagnosis of such cases It has been pointed out repeatedly[3] why this diagnosis is erroneous in the majority of these cases They comprise mostly children with a constitutional type of obesity The characteristic distribution of the adipose tissue in fat boys corresponds to the eunuchoid or the female or the asexual type because the immature testicles do not supply the organism with sufficient amounts of hormone to exert an inhibitory influence upon the lipophilia of some parts of the body. Boys are comparable in this respect to adult men in whom testicular hormone is lacking for such reasons as castration, destruction of the testicles by some pathologic process, atrophy due to pituitary deficiency, or primary hypoplasia (eunuchoidism) Hypoplasia of the genitalia in fat boys is usually apparent rather than actual The penis and scrotum are im-

bedded in a large pad of pubic fat If this pad is pushed back to the root of the penis, it is usually apparent that the genital organs are of normal size

It must be remembered furthermore that the genitalia vary in size in normal individuals They may remain practically stationary in size from birth until the eleventh or twelfth year, at which time a rapid growth begins The younger the boy, the larger proportionately do the genital organs appear, and the nearer he approaches to puberty, the smaller do they seem in proportion to the size of his body The contrast is even more marked in many fat boys who actually exceed the average normal height for their age Even normal-sized prepuberal testicles are likely to appear hypoplastic in large, stout subjects near puberty

It must be granted on the other hand that the percentage [illegible]

[illegible]

justification for explaining clinical symptoms and signs in the prepuberal years on the ground of hypogonadism Castration in that period produces no characteristic signs, it is not until puberty that a defective development of secondary sex characteristics and the typical make-up of primary hypogonadism become apparent The diagnosis of eunuchoidism, as a matter of fact, cannot properly be made before puberty, for the very term implies failure of normal development at puberty as the result of primary testicular hypoplasia

Furthermore, the diagnosis of undescended testicles is frequently not warranted It is justified only after thorough and repeated examination Actually hypoplastic or incompletely descended testicles in obese boys must be considered a sign of endocrine stigmatization, that is, as a coincident manifestation of the abnormal anlage and not as a causal factor in obesity This situation, pointed out in more detail in previous portions of this book, was not always interpreted correctly [10]

The studies of S C Werner,[11] H Bruch,[12] and others[13] resulted in full confirmation of my view that most of the cases of prepuberal obesity are erroneously considered to be endocrinopathies Such cases should not be identified with Froehlich's syndrome

This, however, does not mean that these children need not be treated because they may outgrow their fitness As a matter of fact, they should be treated as cases of obesity, not as cases of Froehlich's syndrome, which they usually are not. In the last few years, obesity has been rightfully included among the problems of *psychosomatic medicine* It seems, however, that the scales balancing the somatic and the mental side have tipped too much in favor of the latter Too much stress is laid on neurotic complexes and maladjustment as etiologic factors in overeating among children [10, 12] The hereditary, constitutional factor is paramount, although largely overlooked or neglected

Mental disorders are frequently attributed to endocrine abnormalities without sufficient justification Spontaneous remissions of psychoses are taken as results of hormonal therapy Recently some cases of dipsomania, dementia praecox, and acute mental confusion during pregnancy were believed to have been due to "cortico-adrenal inadequacy" on the basis of low blood pressure, hirsuties, and large canines [13] The constitutional aspect of such cases is more suggestive of endocrine stigmatization coordinated with the mental disorders There are no convincing arguments proving an endocrine causation of such psychoses Amenorrhea occurring with schizophrenia or during melancholy, and hyperthyroid signs occurring during the manic phase of a cyclic psychosis, may be consequences rather than etiologic factors in such primary mental disorders It does not increase esteem for clinical endocrinology when the author of a well known textbook of endocrinology[20] expresses his belief (in the preface) that such terms as neurasthenia, hypochondria, and the like are obsolete and should be sup-

planted by terms referring to endocrinologic disorders Laymen prefer suffering from "gland trouble" to being called neurotics Endocrinologists, however, should know better

Even in the so-called "experimental neurosis in the sheep and dog," involvement of the endocrine glands has been assumed[14] Confronted with an unusual situation, the trained animals show unusual nervous reactions referable to both the neuromuscular and the autonomic nervous system Not all races and not all animals are equally predisposed to formation of what Anderson and Parmenter[14] call "experimental neurosis" No other result of the painstaking work could have been expected The authors advanced the following working hypothesis

> In summary, the working hypothesis here advanced is concerned with a circle of connected events Repeated and prolonged emotions, incident to the experimental procedure, produce a chronic imbalance of the internal secretions, which induce a constant state of imbalance of the chemistry of the nerve cells A change in the irritability of the nervous system results. The nervous system may become hyperirritable Further and prolonged stimulation of the emotions reinforces and perpetuates the changes in internal chemistry and the vicious circle of events is complete

Is not the criticism on the part of numerous psychologists and clinical psychiatrists fully justified—namely, that these investigators have missed the point, in that they do not concern themselves with the psychology of the animals? The point that the authors missed lies before the facts that they try to explain hypothetically How does the experience of unusual and unexpected situations, of "conflict situations," so to speak, provoke emotions? Since such emotions actually occur under the conditions of the experiment, the hyperirritability of the nervous system is conceivable without reference to internal secretions Emotions result from an irritation of certain portions of the brain and may produce nervous hyperirritability without the interference of hormonal factors Alterations of glandular secretions are known to occur under these circumstances, they represent, however, repercussions of

the hyperirritability of the autonomic nervous system rather than its cause

It is gratifying to hear the warning voices of leading authorities with regard to the outgrowths of vitamin therapy[14] Ruffin[15] states

There is a rapidly growing tendency today to attribute most of the ills of the human race to a deficiency of this or that vitamin The suggestion is being made that the neurotic, the neurasthenic, the mentally retarded, the biologically unfit or constitutional inferiority are often expressions of deficiency states This may or may not be true, certainly it is extremely difficult to prove any causal relationship It is entirely possible that many of them are results of subclinical deficiency states existing since birth

As a matter of fact it may be possible but it is entirely improbable The hereditary nature of these constitutional inadequacies can be demonstrated in most of the instances, while vitamin deficiency can not The disappointing results of Ruffin in the treatment of patients suspected of having a mild deficiency of the known members of the B complex are not in accordance with the vitamin theory Thanks to tremendous commercial propaganda, vitamin therapy has become a powerful psychotherapeutic factor [illegible] ble results must be [illegible] is [16] to this factor

Err [illegible]

sis c [illegible] constitutional disease Rob [illegible] Brucer[17] declare "*Thousands of normal persons are treated for hypotension, and a much larger group in the hypertensive class are given a false sense of security*" We agree with the authors, in so far as essential (constitutional) arterial hypotension does *not require* special *treatment* If *persons with constitutionally low blood pressure need* medical attention it is the psychosomatic *personality*, not the low blood pressure, that has to be taken care of The second part of Robinson's and Brucer's statement, however, involves a danger The danger lies in the creation of unhappiness and hypochondria by inciting unnecessary fear and anxiety

This is all the more true since the authors estimate about 40 per cent of the adult population to be prehypertensive or hypertensive This estimate is made on the ground that a person whose systolic blood pressure reading occasionally exceeds 140 is considered an 'incipient hypertensive" In Robinson's and Brucer's paper we find the blood pressure readings of a man who at the age of 66 had a blood pressure of 110/74, at 67, 146/86, at 69, 132/70, at 70, 146/82, at 73, 114/78, at 74, 144/86, and at 75, 136/80 Was he at 75 still an 'incipient hypertensive'? At what age is he expected to have a full fledged hypertension?

There is no cause for any misunderstanding There is not the slightest doubt that a systolic blood pressure of over 140 in an otherwise healthy individual, particularly in the first four decades of his life, may be suggestive of incipient essential hypertension He may just as well, however, maintain this blood pressure level for decades, up to his old age The diagnosis, prognosis, and subsequent management of such persons depend on thorough study of their individual personalities, and on follow up of their condition for a longer period of time Statistical statements, although based on huge numbers of individuals, are of restricted value with regard to the management of the individual case

To comment on the many pitfalls and errors occurring in endocrine therapy would go beyond the subject this book is dealing with Only so far as they are related to it and as they touch on general principles of hormone therapy may they be briefly mentioned Since we have at our disposal powerful endocrine preparations, it is necessary to be well acquainted with both the indications for use and the possible undesirable side effects of the various preparations It is necessary to know that small and large doses of estrogenic hormone, for instance, may have entirely different effects on the organism The inhibitory action on the anterior pituitary of large doses of estrogenic hormone may counteract the effect desired One must bear in mind that the activity of endocrine glands is

regulated by the requirements of the body. If the body is supplied with a hormone either orally or parenterally for a long period of time, the gland manufacturing this particular hormone in the body is induced to restrict its own activity. First diminution of its function, later atrophy of its parenchyma, may ensue. There is indication that this may occur in the thyroid, parathyroids, ovaries, testicles, thymus, suprarenals, and pancreas.

In cases of hypothyroidism, thyroid preparations must frequently be taken for a lifetime in order to make up for the insufficient production of thyroid hormone. If, however, a 48-year-old woman has been taking from 2 to 4 grains of thyroid every day for twenty-eight years because of constitutional obesity, hypothyroidism will be the result of such a treatment. The constitutional nature of this particular case of obesity is suggested by the fact that the patient's brother has a body weight of 240 pounds. It is unwise in such cases to prescribe thyroid in small doses to be taken for such long periods of time. In order to obtain the desired defattening result, it is preferable to use large doses of thyroid intermittently—for example, administering it for from four to five days, at intervals of from five to ten days.[13] There is nothing astonishing about the fact that a functional disorder of the ovary, insignificant as it may be, will not be improved after fifteen years or more of continuous administration of estrogenic hormone.

It must be kept in mind that although we are supplied with the most perfect and valuable endocrine preparations, we are not able to adjust their administration to the requirement of the body as precisely as the production and liberation of hormones is adjusted to the requirement in the normal body. It is beyond our power to imitate exactly the nervous factors that regulate the discontinuous production and output of hormones under normal conditions. We should be modest and more reluctant to interfere with the precise mechanism of the living machine without necessity. One of the most difficult tasks in medicine is: *Primum non nocere!*

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